Detecting Signals of Electrocardiogram QT prolongation and QT shortening: Regulatory Implications

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This work is dedicated to the little boy who stole my heart.

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Abstract

Drug-induced changes to the conductivity of the human ether-a-go-go related gene (hERG) potassium channels, affect cardiac repolarisation and put patients at risk of fatal cardiac arrhythmias such as Torsade de Pointes. Healthcare professionals and patients benefit from knowing which medicinal products cause this adverse event, in order to minimise co-prescribing of such drugs or to carry out appropriate monitoring.

The aim of this study was to detect and characterize the QT change liability of authorised medicinal products. The methodology was in two parts. Study 1 involved extracting signals from the Eudravigilance database, and in study 2 an in-depth assessment of unexpected signals through review of literature, preclinical, adverse drug reaction and clinical trial data was performed. Proportional reporting ratios were used to identify statistical associations between drugs and QT change and expectedness was checked through the product information (PI). A list for the frequency of expectedness was created. Drugs not expected to cause QT changes were evaluated within the Bradford-Hill criteria for association.

Four hundred and seventeen candidates with a potential signal of QT modulation were identified. Of these, 12 products did not have QT change as an expected adverse event and so were assessed. Results from the assessment showed that changes to the PI of mirabegron, asenapine and pantoprazole could be warranted and signals on QT prolongation for mirabegron and asenapine were reported to the European Medicines

Agency's Pharmacovigilance Risk Assessment Committee (PRAC). In March 2017, the PRAC rapporteurs for these active substances (Spain and United Kingdom) agreed to take regulatory action and update the SPCs within the next periodic safety review procedures, starting in quarter four 2017. For pantoprazole, an emergent signal of hypokalaemia may warrant further separate investigation. For QT shortening, fingolimod and olanzapine were assessed, and the data for these two drugs did not lead to a recommendation for change to the PI due to lack of robust evidence.

In conclusion, this study presents a number of outputs; (1) inferences on (a) mirabegron, (b) asenapine and (c) pantoprazole, (2) assessment recommendations for preclinical assessors and marketing authorisation holders looking at hERG studies, (3) reflections on the pharmacological basis of short QT, and (4) an innovative proposal for a QT drugs list with risk categorisation.

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List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic Drugs
ADR	Adverse Drug Reaction
BH	Bradford Hill Criteria
BrS	Brugada Syndrome
CAP(s)	Centrally Authorised Product
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
COX-2	Cycloxygenase-2 enzyme
CPVT	Catecholaminergic polymorphic ventricular tachycardia
diLQT	Drug-induced Long QT
diLQTS	Drug-induced Long QT syndrome
diSQT	Drug-induced Short QT
diSQTS	Drug-induced Short QT syndrome
EC	European Commision
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
EV	Eudravigilance
EVDAS	Eudravigilance Data Analysis Software
HEK293	Human Embryonic Kidney Cells
hERG	Human Ether-a-go-go Related Gene
Ikr	Rapid delayed inward rectifier potassium current
Iks	Slow delayed inward rectifier potassium current
LQTS	Long QT Syndrome

MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Malta Medicines Authority
MRC	Medicines Review Committee
NAP(s)	Nationally Authorised Products
OTC	Over-the-counter
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fredericia formula
QTcB	QT interval corrected for heart rate using Bazetts formula
QTs	QT shortening
QTp	QT prolongation
RMP	Risk Management Plan
SmPC/SPC	Summary of Product Characteristics
SAE	Serious Adverse Event
SCD	Sudden cardiac death
SQTS	Short QT syndrome
TdP	Torsade de Pointes
UK	United Kingdom
USA	United States of America

Glossary

Adverse drug reaction (ADR); *synonyms: Adverse reaction, Adverse effect, Undesirable effect*

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (European Medicines Agency, 2014).

Council for International Organizations of Medical Sciences form (CIOMS)

The CIOMS form is the form contained in the final report of the CIOMS I working group on international reporting of adverse drug reactions corresponding to the minimum standard of information required to submit a report. The form may be downloaded from the CIOMS website (CIOMS, 2010).

Direct healthcare professional communication

A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product (European Medicines Agency, 2012).

Eudravigilance; *synonyms: Eudravigilance database*

EudraVigilance is the European data storage, processing network and management system, which has been developed according to internationally agreed standards and allows the EMA to manage the electronic data exchange of Individual Case Safety

Reports (ICSRs) and to support the pharmacovigilance activities at Community level (European Medicines Agency, 2015).

European Pharmacovigilance Issues Tracking Tool (EPITT)

EPITT is a webbased system that tracks and monitors the safety of medicinal products regardless of their authorisation type. The objectives include the monitoring of life-cycles of a sub-set of safety signals and safety issues discussed at the level of the Pharmacovigilance Risk Assessment Committee (PRAC), the tracking of the Periodic Safety Update Report (PSUR) cycles and timetables assessments in the context of the PSUR Work Sharing project, and Risk Management activities (European Medicines Agency, 2012).

Expectedness

Whether an adverse event is known to occur with a medicinal product and is therefore listed in the product information (ICH E2A, 1995).

Frequency of expectedness

How commonly or rarely an adverse event is expected to occur with a medicinal product. Frequency categories are defined in the SPC as follows;

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Frequency unknown (cannot be estimated from the available data) (European Medicines Agency, 2014).

Generic medicinal product

A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies (European Medicines Agency, 2014).

Healthcare professional

For the purposes of adverse drug reaction reporting, suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners (European Medicines Agency, 2012).

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest (European Medicines Agency, 2012).

Important identified/potential risks

An identified risk or potential risk is one that could have an impact on the risk-benefit balance of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important (European Medicines Agency, 2012).

Individual case safety report (ICSR); *synonym: Adverse (drug) reaction report*

Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time (European Medicines Agency, 2015).

Labelling

Information on the immediate or outer packaging of a medicinal product (ICH E2A, 1995).

Medicinal product

Any substance or combination of substance presented as having properties for treating or preventing disease in human beings; or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (ICH E2A, 1995).

Minimum criteria for ADR reporting

For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product (CIOMS, 2010).

Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant (European Medicines Agency, 2012).

Misuse of a medicinal product

Situations where the medicinal product is intentionally and inappropriately used, not in accordance with the authorised product information (European Medicines Agency, 2012).

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU (European Medicines Agency, 2012).

Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information (European Medicines Agency, 2012).

Package leaflet

A leaflet containing information for the user which accompanies the medicinal product (European Medicines Agency, 2012).

Periodic safety update report

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase (European Medicines Agency, 2013).

Pharmacovigilance

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (European Medicines Agency, 2012).

Pharmacovigilance Risk Assessment Committee (PRAC)

Committee at the European Medicines Agency responsible for assessing and monitoring safety issues related to medicines for human use (European Medicines Agency, 2012).

Post-authorisation safety study

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures (European Medicines Agency, 2013).

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed (ICH E2A, 1995).

Product Information

The summary of product characteristics and the package leaflet of a medicinal product (European Medicines Agency, 2012)

Proportional Reporting Ratio (PRR)

For a given medicine, the proportional reporting ratio is the proportion of all reactions to a drug which are for a particular medical condition of interest, compared to the same proportion for all drugs in the database, in a 2 x 2 table (European Medicines Agency, 2012)

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as regards patients' health or public health (European Medicines Agency, 2012).

Risk Management Plan (RMP)

A detailed description of the risks and the management planning system for a product (European Medicines Agency, 2012).

Risk minimisation activity *synonym: Risk minimisation measure*

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur (European Medicines Agency, 2012).

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect (CIOMS, 2010).

Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (European Medicines Agency, 2012).

Spontaneous report

An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme (ICH E2A, 1995).

Summary of product characteristics

A summary of the drug dossier, it is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics (European Medicines Agency, 2012).

Chapter 1: Introduction

1.1 Background

Over half a century has passed since the thalidomide tragedy, and more recently, discoveries of cardiovascular and hepatobiliary risks associated with cyclooxygenase-2 inhibitors such as rofecoxib[1] and lumiracoxib[2]. These issues have sensitized the medical community to the adverse risks inherent to medicinal product use, and to the importance of vigilantly watching for new signals as they may arise in a product's lifecycle. Adverse events are mostly highlighted during the testing of a new drug, however experience has shown that they can affect patient safety long after a medicinal product has been approved for general use (Finney, 1963; Bibawy et al, 2013; Kotasek et al, 2014, Chui et al 2016). This risk is greatest when screening for adverse events during early preclinical or clinical development is incomplete. Complete profiling of adverse events is dependent on the insights of the complex mechanisms of action studied and knowledge into drug safety will not keep pace with the introduction of novel medicinal products with new mechanisms of action (Finney, 1963; FDA, 2011). The early detection of effects of medicinal products at the molecular level, and the use of rapid warning systems to convey information to healthcare professionals and patients is consequently, of great importance (Finney, 1963).

The main objective of signal detection is to identify unrecognized adverse drug events outside the controlled environment of clinical trials. Considered to be the most important aspect of current drug surveillance systems, signal detection is the essential first step to

[1] European Medicines Agency. EMEA statement following withdrawal of Vioxx (rofecoxib). 2004; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015262.pdf.

[2] European Medicines Agency. Novartis withdraws its marketing authorisation application for Joicela (lumiracoxib). 2011; Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/04/news_detail_001246.jsp&mid=WC0b01ac058004d5c1

minimizing preventable human morbidity and mortality caused by unwanted effects of medicines (Grundmark et al, 2014; Kumar and Khan, 2015).

1.2 Importance of signal detection on the QT interval

The QT interval is an established biomarker for the risk of cardiac arrhythmias (Farkas and Nattel, 2010; Konigstein et al, 2016; Schwartz and Woosley, 2016; Tisdale, 2016). Drug-induced arrhythmia often presents as life-threatening ventricular tachyarrhythmias, Torsade de Pointes (TdP) or sudden cardiac death (Crotti and Schwartz, 2014; Villamanan et al, 2015; Michels et al, 2016; Roden, 2016; Schwartz and Woosley, 2016; Tisdale, 2016). Results from a large case control study of over 6000 patients showed that using QT-prolonging drugs doubled the risk of sudden cardiac death, especially in women and patients who had recently started treatment (Straus et al, 2005). In patients treated with antipsychotic agents the risk of sudden death was shown to be threefold (Reilly et al, 2000; Reilly et al, 2002).

In older patients, 65 years and over, a prolonged QT-interval appears to be associated with a higher all-cause and coronary heart disease mortality (Robbins et al, 2003) and concurrent use of more than one QT-interval prolonging drug is considered a risk factor for TdP (Roe et al, 2003; Allen LaPointe et al, 2006; Freeman et al, 2008). In a study in patients with a QT interval prolongation >550ms, medications were the attributed cause in 48% of cases and involved two or more QT-drugs in 25% of the cases (Laksman et al, 2015). In critically ill patients co-prescribing of QT-drugs occurred in 18.6% of the patients

and was associated with a higher mortality rate and longer duration of hospitalization (Freeman et al, 2008).

Drug-induced Long QT (diLQT) has led to several post-marketing drug withdrawals of commonly used medicinal products, such as thioridazine, cisapride and astemizole after many years of these products being marketed.

Molokhia and colleagues have shown that failure to appreciate the magnitude of risk of diLQT has led to delays in drug withdrawals. In their study, only 3 of 40 ascertained cases of LQTS were actually identifiable though cardiology records and reported through pharmacovigilance systems. They emphasised that prolonged QT, which degenerates into a ventricular tacchyarrythmia, is likely to go undiagnosed if cases do not survive and argue that gathering superfluous evidence may impede timely action since the eventual withdrawal of thioridazine in June 2005 was long after the association had been described (Molokhia et al, 2008).

Substantial efforts have been made over the years to identify drugs which affect the QT interval in order to prevent administration of such drugs in patients with known risk factors. The webpage, CredibleMeds®[3] provides an established list of QT-prolonging drugs which are licensed in the USA (Woosley et al, 2017). In this list, the risk of QT prolongation is directly correlated to the risk of TdP and medications are placed in three different risk categories; "Known, Possible or Conditional risk of TdP", based on the level of evidence supporting the association between the drug and the adverse events of QT prolongation and TdP (Woosley et al, 2017). In Europe, there exists no officially approved list of QT-prolonging drugs and considering that there are medicinal products marketed in the EU but

[3] https://www.crediblemeds.org/

not in the USA, not all EU products may be listed in CredibleMeds® (Woosley et al, 2017). In Europe, the information on whether a medication is expected to cause QT prolongation or not is found in the Summary of Product Characteristics (SPC).

Other studies have reported that the scientific community is missing an elusive link and that QT interval change is often reported as having unexplained inter-individual variability (Tisdale, 2014; Le Guennec et al, 2016). According to Zareba (2007), challenges related to accuracy in measurement of the QT interval and optimal heart rate corrections render the value of QTc low in terms of predictability of arrhythmia risk while Couderc and Lopes (2010) have published instances where arrhythmia occurred during the presence of normal duration of the QT/QTc interval.

In a meta-analysis of 19 large cohort studies by Zhang and colleagues, where the implications of small variations in QT-interval length (within the normal limits) on mortality in the general population were questioned, it was compellingly shown that there was a consistent association between prolonged QT interval and the risk of total, cardiovascular, coronary, and sudden cardiac death (Zhang et al, 2011). This meta-analysis also showed that changes to the QT-interval length are determinants of cardiac health and mortality in the general population.

1.3 History of QT prolongation and Torsade de Pointes

Schwartz et al (2016), describe how a single case report on quinidine syncope, in 1923 triggered the story of QT interval prolongation and TdP (Schwartz et al, 2016). It took forty years, in 1964, for several other case reports to be published on quinidine and TdP (Clark-

Kennedy, 1923; Selzer and Wray, 1964; Reynolds and Vander Ark, 1976) and the link to be made, that is, that the syncope events had 2 key characteristics in common; QT interval prolongation and an unusual arrhythmia named TdP.

Torsades de pointes ("twisting of the points") was described by the French cardiologist Dessertenne (1966), referring to the electrocardiographic pattern of a ventricular tachyarrhythmia (Figure 1.1).

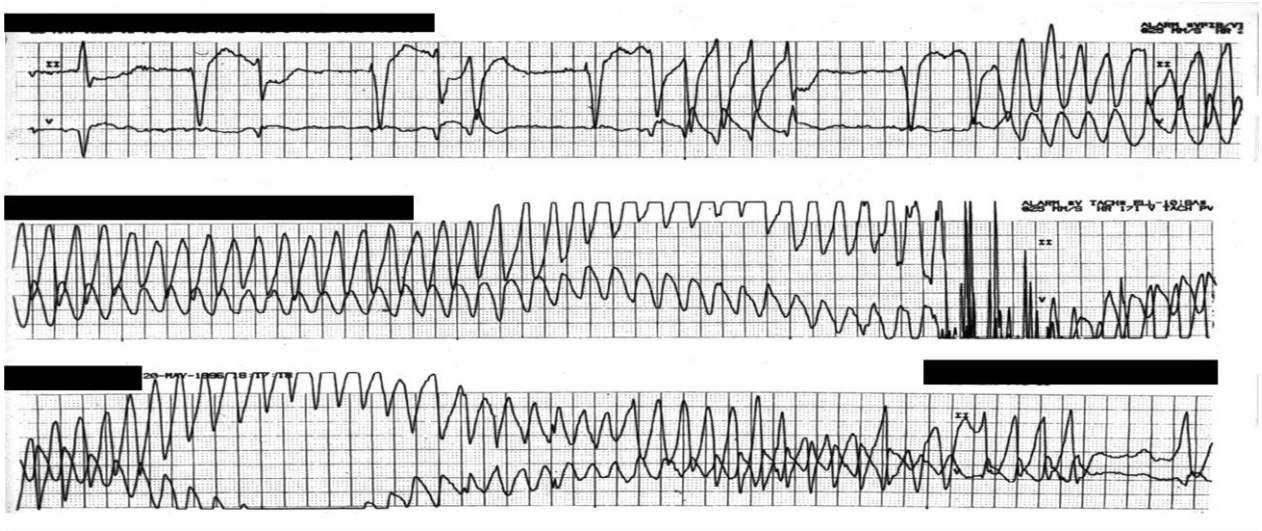


Figure 1.1 ECG trace developing TdP

Reproduced from:

Drew BJ et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010 Mar 2; 121(8):1047-1060

Dessertenne (1966) noted the association of TdP with a markedly prolonged QT interval. As most of the initial cases of TdP reported in the 1970s and 1980s were observed in patients treated for cardiac arrhythmia, it was assumed to be limited to antiarrhythmic drugs, such as quinidine and procainamide. However in 1990, the medical community was

alerted that TdP could also occur with non-cardiac drugs taken by millions of patients, such as the non-sedating antihistamine terfenadine (Schwartz and Woosley, 2016). Up to that time, neither clinical practice nor drug development was affected by the association of drug therapy with QT interval prolongation (Roden, 2016).

During the same year (1990) terfenadine was being considered for over-the-counter (OTC) status when a case report of TdP in association with its use was published by Monahan et al (Monahan et al, 1990). Studies over the next years elucidated the mechanism by demonstrating that terfenadine at therapeutic dosages in healthy subjects produced minimal prolongation of the QT interval, but that in the presence of other factors such as liver impairment, overdose, or co-administration of drugs inhibiting the extensive presystemic metabolism of terfenadine, plasma concentrations of the drug rise dramatically and marked QT prolongation occurs (Honig et al, 1993; Woosley et al, 1993). Terfenadine was not granted OTC status and was withdrawn from the market (Hondegem et al, 2011).

Shortly after, reports emerged of TdP with another antihistamine, astemizole, followed by the gastrointestinal drug cisapride, the antibiotic erythromycin, the opiates levomethadyl and methadone, a drug for hypercholesterolemia, probucol, and many other nonantiarrhythmic drugs, including antifungal agents, antinausea and anticancer drugs (McComb et al, 1984; Botstein, 1993; Kornick et al, 2003; Schwartz and Woosley, 2016). It became clear that TdP was a possibility even with non-cardiac drugs in various therapeutic classes (Schwartz et al, 2016).

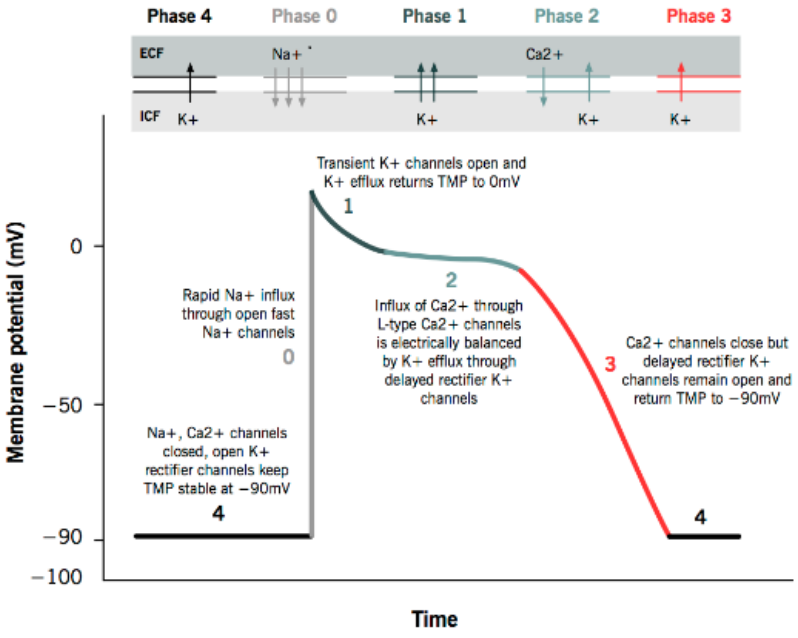
1.4 History of QT shortening

Genetic short QT, was named as a new clinical syndrome by Gussak et al in 2000, when three members of one family; a 17-year-old girl requiring cardioversion for paroxysmal AF, her 21-year-old brother and 51-year-old mother all displayed QT intervals of 272 ms or less at normal heart rates (Shah, 2010). A few years later, other reports of families with congenital forms of short QT interval associated with arrhythmias and sudden cardiac death started to be reported in the literature (Gaita et al, 2003; Frea et al, 2015). In 2004, Brugada and colleagues reported the first gene responsible for Short QT syndrome (SQTS) (Brugada et al, 2004).

In 2010, Shah, a medical assessor at the UK Medicines and Health Regualtory Agency (MHRA), reported reviewing non-clinical and clinical evidence within drug dossiers being submitted for approval in the UK, which suggested that QT interval shortening could also be an unintended drug effect, proarrhythmic, hence, a medication safety concern (Shah, 2010). While drug companies were running tests in line with ICH guidelines (S7B and E14) to detect QT prolongation, a number of drugs that shorten the action potential duration in repolarization assays and shortened the QT interval were being observed (Shah, 2010). According to Shah, rufinamide, a triazole derived anticonvulsant and designated as an orphan drug, is the first QT-shortening drug to be approved in the post-ICH E14 days (Shah, 2010). Rufinamide was found to have no effect on hERG current when investigated in human embryonic kidney cells, however QTc interval shortening was seen with an increase in dose, which demonstrated clearly a biological gradient for drug and effect (Shah, 2010).

1.5 Cardiac electrophysiology

The electrophysiology of the heart has been extensively studied and described (Brown and Kozlowski, 1997). Hillary Brown and Roland Kozlowski in their book on the physiology and pharmacology of the heart, describe the generation of excitatory stimuli and action potentials in individual cardiomyocytes (Brown and Kozlowski, 1997). Action potentials form as a result of the gating of ion channels in the cell membrane which permit different inflow and exit of ion currents, thereby creating the changing phases of the action potential (Brown and Kozlowski, 1997). Figure 1.2 shows the action potential in a single cardiac myocyte and its dependence on the influx and efflux of ions for a change in voltage.



* TMP - Transmembrane potential

Figure 1.2 Action potential and ionic flux in a single cardiac myocyte

Reproduced from: Baruscotti M et al. Physiology and pharmacology of the cardiac ("funny") current. Pharmacol Ther 2005 Jul;107(1):59-79.

The action potential starts with a large inward current of sodium ions (INa) which rapidly depolarizes the cell. This is followed by the plateau phase with influx of calcium ions through L-type calcium channels (ICa) and outward repolarizing potassium currents (IK). Further efflux of potassium follows which restores the resting membrane potential (Titier et al, 2005).

1.5.1 Potassium channels

The repolarisation phase of the myocytes is largely driven by the outward movement of potassium (K+) ions (Yap and Camm, 2003). Two important inward K^+ currents participating in ventricular repolarisation are the subtypes of the delayed rectifier current, IKr (rapid) and IKs (slow) (Yap and Camm, 2003). The IKr (rapid) ion conducting channel is also known as the human-ether-a-go-go related gene (hERG) channel. Blockade of either of these outward potassium currents prolongs the action potential and the QT interval (Yap and Camm, 2003), while augmenting the outward current of potassium ions causes shortening of the action potential and the QT interval (Van Houzen et al, 2008).

The hERG channel is the most susceptible to pharmacological influence (Brown and Kozlowski, 1997; Sperelakis et al, 2001; Ahmad and Dorian, 2007) and in the majority of cases, is at least in part responsible for the pro-arrhythmic effect of active substances (Yap and Camm, 2003; Ahmad and Dorian, 2007; Altmann et al, 2008; Amin et al, 2010). Introducing a 50% hERG-channel current block, results in 8% prolongation of the action potential duration (Zemzemi et al, 2013).

1.5.2 Cardiac electrophysiology in inherited disease

The importance of ion channels in maintaining normal heart rhythm is reflected by the manifestation of arrhythmias in inherited diseases, caused by gene mutations, encoding ion channels (Jost et al, 2015). The four main cardiac ion channelopathies are the: (1) long QT syndrome (LQTS), (2) Brugada syndrome (BrS), (3) short QT syndrome (SQTS), and (4) catecholaminergic polymorphic ventricular tachycardia (CPVT) (El-Sherif and Boutjdir, 2015). Together, these channelopathies are responsible for about 10% to 15% of Sudden Cardiac Death (SCD), mostly in young patients, which occurs in the presence of a structurally normal heart (Amin et al, 2010). Much of the scientific understanding of drug induced QT prolongation comes from the study of the inherited congenital disease LQTS. (Brown and Kozlowski, 1997; Sperelakis et al, 2001; Amin et al, 2010).

LQTS arises from mutations of genes that encode the protein channels for IKr, IKs and Na (Ching and Tan, 2006). According to Roden and Nachimutu, in acquired (drug-induced) LQTS, the mechanism is predominantly due to blockage of the IKr channel, hERG as it conducts a potassium current which is critical to the phase 3 repolarization of the cardiac action potential (Roden and Viswanathan, 2005; Nachimuthu et al, 2012). Medications that prolong the QT interval are able to act on hERG due to its distinct molecular structure, which has a long vestibule, facilitating the attachment of drug to channel (Nachimuthu et al, 2012).

Inherited mutations (loss of function) of the hERG gene lead to type-2 LQTS (Nachimuthu et al, 2012). Ten different types of congenital type LQTS have been described (Modell and Lehmann, 2006; Roden, 2008; Hedley et al, 2009). LQT1, LQT2, and LQT3 account for the majority of the cases of congenital LQTS (Nachimuthu et al, 2012). LQT1, the most

common of the three, is caused by mutations in the KVLQT1 (also called KCNQ1) gene (Nachimuthu et al, 2012) and is known to be triggered by exercise. LQT2 is caused by a variety of mutations in the hERG which may involve the pore or non-pore region of the hERG channel. Pore mutations carry high risk for cardiac events and may affect young patients (Moss, 2006), whereas non-pore mutations often lead to TdP in the presence of hypokalemia (Berthet et al, 1999; Nachimuthu et al, 2012).

1.5.3 The QT interval

The QT-interval (Figure 1.3) represents the time taken for the ventricles of the heart to depolarise and then repolarise and is thus an indicator of the ventricular action potential duration (Le Guennec et al, 2016).

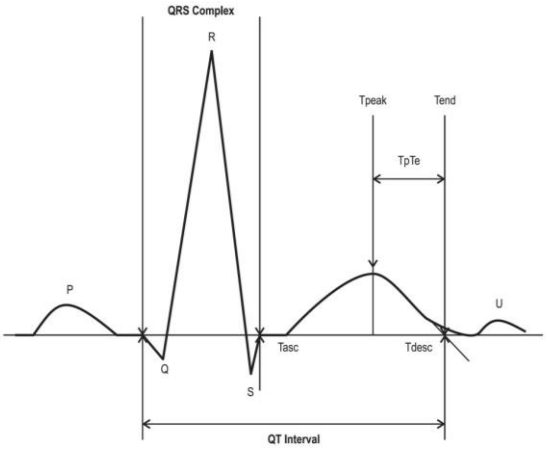


Figure 1.3: Representation of ECG trace in sinus rhythm showing the QT interval

Reproduced from:

Ozgur K et al. Evaluation of Electrocardiographic T-peak to T-end Interval in Subjects with Increased Epicardial Fat Tissue Thickness. Arq. Bras. Cardiol; 105(6): 566-572.

1.5.4 Measurement of the QT interval

On 12-lead ECG, the QT interval is measured from the beginning of the QRS complex to the end of T wave as it returns to baseline (Nachimuthu et al, 2012). Manual measurements of the QT interval should be taken from leads II and V5 or V6 as these leads have the greatest positive and negative predictive value in detecting abnormal QT intervals (Monnig et al, 2006). Holter monitor ambulatory readings are sometimes used to get a 24/48hour picture of a patient's electrical activity of the heart via continuous monitoring. Some controversy about the value of its use exists. Nachimuthu et al (2012) report that since there are no standards for interpreting prolonged QT intervals from Holter ambulatory monitoring, QT assessment using this method is not recommended.

Since the QT interval naturally shortens or prolongs, depending on the heart rate, many methodologies for correcting QT intervals for heart rate have been proposed (Nachimuthu et al, 2012). There is no consensus as to which method is the most effective, however, the most universally adopted method is Bazett's formula ($QTc = QT/\sqrt{RR}$ in seconds) that provides an adequate correction for heart rate ranging between 60 and 100 beats/min (Nachimuthu et al, 2012). At low and high heart rates, this method has been reported to underestimate and overestimate the QT interval (Aytemir et al, 1999). At heart rates outside normal range, other correction methods such as Fredericia ($QTc = QT/(RR)1/3$) or Framingham ($QTc = QT + 0.154(1 – RR)$ should be utilized (Aytemir et al, 1999).

1.6 Long QT presentation and diagnosis

Initial presentation of Long QT syndrome (LQTS) occurs in the majority of cases, after a patient experiences syncope or cardiac arrest (Crotti and Schwartz, 2014; Mazzanti et al, 2014; Spears and Gollob, 2015). Diagnostic LQTS values are >450 in males and >470 in females (Johnson and Ackerman, 2009). Triggers for an event of QT prolongation vary according to the different channelpathy and may include exercise, swimming, emotion and loud noises but may also occur during sleep (Crotti and Schwartz, 2014; Mazzanti et al, 2014; Spears and Gollob, 2015). Medications may also affect the QT interval as discussed in section 1.3 (Crotti and Schwartz, 2014; Mazzanti et al, 2014; Spears and Gollob, 2015).

Information about which medication the patient has taken is critical for the differential diagnosis of congenital LQTS and of drug-induced QT prolongation. In the majority of LQTS cases, an immediate family history of cardiac arrest and sudden death, will be present (Johnson and Ackerman, 2009).

1.6.1 Genetics of long QT

Currently, three LQTS genes form the major genetic variants for congenital LQTS; KCNQ1, KCNH2, and SCN5A, and are responsible for 75% of the disease (Tester and Ackerman, 2014). Another 10 variants collectively account for less than 5% of LQTS cases (Tester and Ackerman, 2014). For the major LQTS genotypes, genotype-phenotype correlations specific gene triggers, patterns on the ECG as well as different responses to beta-blockers which are the main therapy used, have been identified (Tester and Ackerman, 2014; Behere and Weindling, 2015).

1.6.2 Risk factors for QT prolongation

Patients at a higher risk of genetic or drug-induced long QT syndrome include those presenting with unexplained fainting, unexplained near drownings or other accidents, unexplained seizures, or a history of cardiac arrest (Tisdale, 2016). Advanced age, female sex, acute myocardial infarction, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, hypocalcemia, hypothermia, bradycardia, treatment with diuretics, elevated plasma concentrations of QTc interval-prolonging drugs due to drug interactions, inadequate dose adjustment of renally-eliminated drugs in patients with kidney disease and rapid intravenous administration have all been cited as risk factors for QT prolongation leading to arrhythmia (Schwartz and Woosley, 2016, Tisdale, 2016). The QT interval is also influenced by the physiologic and metabolic state of patients (Skinner et al, 2014). In diabetics for example, it is hypothesized that sudden deaths in the form of "dead-in-bed syndrome" are linked to the lengthening of the QTc interval during nocturnal hypoglycemia (Kubiak et al, 2010; Nordin, 2014; Skinner et al, 2014).

1.7 Short QT presentation and diagnosis

QTc values below 330 ms are considered diagnostic (Khera and Jacobson, 2015). Values below 350 ms for males and 360 ms for females are considered suspicious in the presence of a pathogenic mutation, a family history or a previous cardiac arrest in the absence of other heart disease (Shah, 2010). It has been suggested by Shah, that a delta shortening of 80ms in any patient may also place the patient at considerable risk (Shah, 2010).

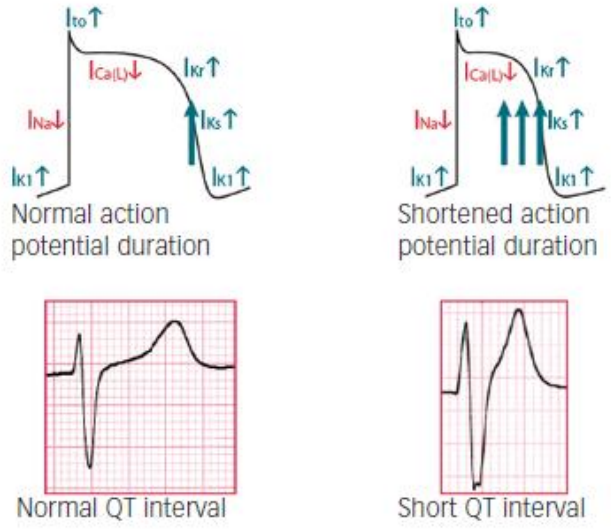


Figure 1. 4 Shortened QT interval and the action potential change due to gain in function of potassium+ channels and loss of function of calcium channels.

Reproduced from: Spears DA, Gollob MH. Genetics of inherited primary arrhythmia disorders. Appl Clin Genet 2015; 8:215-233.

Van Houzen et al (2008) in their review of the Short QT Syndrome (SQTS) report sudden cardiac death, syncope, and ventricular fibrillation as the events most likely to be reported at presentation of SQTS. Other more minor events such as dizziness, palpitations, lightheadedness, and paroxysmal atrial fibrillation have also been described (Van Houzen et al, 2008). Sudden cardiac death is the first symptom in the majority of cases and first clinical presentation (Van Houzen et al, 2008; Brugada et al, 2014; Mazzanti et al, 2014; Rudic et al, 2014). A family history of sudden cardiac death is often present, occurring in immediate relatives of any age (Van Houzen et al, 2008; Brugada et al, 2014). The mean age at diagnosis is 30 years (Giustetto et al, 2006), but ages as low as infancy have been

reported, with Morphet suggesting that sudden infant death syndrome may be due to short QT (Morphet, 2007).

Identification of patients with short QT syndrome is not expected to be easy due to its highly malignant nature, with patients often dying before making it to hospital. Due to the high rate of deaths in young patients, the defective genes are often not transmitted to any progeny (Rudic et al, 2014). Brugada and colleagues describe SQTS as a self-extinguishing condition (Brugada et al, 2014). In a single study with 29 patients diagnosed with short QT syndrome, 3 patients died before clinical evaluation and another 6 patients had resuscitated cardiac arrest. 10 patients had cardiac arrest and in 8 patients this was the initial presentation (Giustetto et al, 2006b). In this study, the survival from cardiac arrest from birth to 40 years was estimated to happen in only 14 patients (Giustetto et al, 2006).

Conversely, data from over 10,000 adults suggest that the prevalence of short QT without the syndrome is possible, and individuals with QTc <320 ms who reached adulthood without developing life-threatening arrhythmias have been reported (Gallagher et al, 2006; Funada et al, 2008). Anttonen et al. reported a low rate of all-cause mortality in individuals with QTc intervals <320 ms (Anttonen et al, 2007), however, since only middle-aged subjects were included, the findings may not be applicable to a younger population. In another study investigating over 18,000 patients, the prevalence of a short QT interval defined as less than 320ms was 0.1% and had the strongest association in males and Afro-Caribbeans (Dhutia et al, 2016). During a follow-up period of 5.3±1.2years, there were no deaths in this group (Dhutia et al, 2016). In this study only patients up to the age of 35 years were included and followed up and it was postulated by Dhutia et al that while long

QT risks increase with age and female sex, it may very well be that short QT may have a risk attenuating effect with age, and a predominance in the male sex.

1.7.1 Genetics of short QT

Short QT syndrome involves at least three different gene mutations of potassium channels involved in repolarization. QT syndrome 1 (SQTS-1), the KCNH2 gene, or hERG, has two missense mutations, that leads to a gain-in-function and shortening of the action potential duration (Brugada et al, 2004; Cordeiro et al, 2005). In SQTS-2, a missens in the KCNQ1 gene encoding the ion channel responsible for the slowly activating potassium channel IKs results in accelerated activation kinetics consistent with a gain-in-function in the outward current. This mutation also leads to shortening of the action potential and is considered the sporadic form of short QT syndrome (Bellocq et al, 2004; Hong et al, 2005). A mutation to KCNJ2 gene encoding proteins responsible for the inward potassium current (IK1) leads to generation of electrical currents that do not decrease to the extent of normal potassium channels and lead to an acceleration of late repolarization and shortening of the action potential (Van Houzen et al, 2008).

1.7.2 Risk factors for QT shortening

Genetic factors affecting short QT have been described elsewhere (see section 1.7.1). For acquired short QT, risk factors reported are sinus tachycardia, hyperthermia, hypocalcemia, acidosis, hyperkalemia, and digoxin therapy (Brugada et al, 2005; Van Houzen et al, 2008).

1.8 Preclinical QT interval testing methods

Since arrhythmias are rarely observed in clinical trials, the QT interval in the ECG is one of the main biomarkers used in the assessment of cardiac safety. Preclinical assessment of cardiac compounds aims at detecting drugs that would require clinical thorough QT studies in line with ICH E14 Guidelines (ICH E14, 2005).

Zemzemi (2013) has concisely and clearly described the different testing strategies commonly applied to assess drug cardiac safety and include:

- Ion channel binding assays to determine binding affinity between drug and cardiac ion channels; (Pugsley et al, 2008)
- Voltage-clamp analysis of ion-channel currents (in particular the hERG potassium channel; see (Curran et al, 1995; Vandenberg et al, 2001; Redfern et al, 2003; Sanguinetti and Tristani-Firouzi, 2006; Hancox et al, 2008)
- Recording of the action potential in isolated myocytes and tissue; (Redfern et al, 2003; Sanguinetti and Tristani-Firouzi, 2006; Hancox et al, 2008)
- Measurement of drug-induced changes to the QT interval in small, and large, mammals (Fossa et al, 2002).

1.8.1 *In vitro* studies

There are four broad categories of *in vitro* models (1) heterologous expression systems, (2) disaggregated cells (studied acutely or in culture), (3) isolated tissues, and (4) isolated intact Langendorff-perfused heart (Zemzemi et al, 2013).

Many preclinical studies use human embryonic kidney cells (HEK293), mouse fibroblasts (C cells) and Chinese hamster ovary cells, all of which have relatively little endogenous voltage-gated channel activity (Obers et al, 2010). *The Xenopus laevis* oocytes microinjected with ion channel RNA is another well-established method for heterologous expression (Obers et al, 2010; Zemzemi et al, 2013). Measurement of ionic currents is performed using two-electrode recording to a voltage clamp. When such models are used, the effects of at least four different drug concentrations are tested and the IC50, the concentration at which 50% inhibition occurs, of both the parent compound and its metabolites is determined (Zemzemi et al, 2013).

While the disaggregated cell is ideal for studying ion currents, action potentials are better studied using isolated tissues (Coronel et al, 1997). Isolated tissues selected should be on the basis of adequate data that demonstrates similarity with human material (Coronel et al, 1997). The species most frequently used are dog, rabbit, and guinea pig (Zemzemi et al, 2013). Canine mid-myocardium and Purkinje fibers appear most susceptible to the effects of hERG block (Janse et al, 1985).

Endo- and epicardial muscle should be studied to ensure that the potential for dispersion is explored (Antzelevitch et al, 1999). To compare the effects of study drug and to validate the study, one of the known strong hERG blockers such as cisapride or moxifloxacin is used for comparison. Studies should account for gender differences especially since it is known that females are more susceptible to QT prolongation and arrythmogenesis (Darpo et al, 2014). For screening large numbers of compounds, the Langendorff-perfused guinea pig or rabbit heart studied with electrogram or monophasic action potential recording techniques, gives consistent information on hERG blocking drugs, compared to standard

compounds (Pinney et al, 1995; Eckardt et al, 1998). Excess prolongation of repolarization in this model, indicates potential problems caused by the drug (Pinney et al, 1995; Zemzemi et al, 2013). Failure to see excess action potential prolongation does not, however, provide complete security in excluding the risk of TdP (Zemzemi et al, 2013). As documented by Zenzemi et al (2013), within these Langendorff studies one is unaware of the potential effects of metabolites, which are an unknown, but important aspect to consider when investigating secondary drug effects. Effects of the new chemical entities on sinus rhythm should be carefully screened as K+ channel blockers frequently cause bradycardia (Zemzemi et al, 2013). TdP-like tachyarrhythmias can be induced in the isolated rabbit heart by reproducing conditions and circumstances that are clinically known to be associated with an increased risk of developing TdP such as hypokalemia and bradycardia (Zabel et al, 1997; Johna et al, 1998).

1.8.2 *In vivo* models

In vivo models can be studied using multi-lead ECG recordings in conscious or anaesthetised guinea-pigs, rabbits, dogs or pigs (Carlsson et al, 1990; Carlsson et al, 1997; Sosunov et al, 1999). As in humans, QT duration should be measured ideally from at least three successive beats. In dogs, T-wave morphology is highly variable which limits the possibility to study serial drug-induced changes in repolarization, unless rigorous attention is paid to maintaining the animal in the same position each time it is studied. Equations to correct QT duration for heart rate can be used, although the accuracy of the correction algorithms varies in different animal models (Detweiler et al, 1977). More information can

be obtained using QT–RR plots on various doses, or by pacing the heart at a constant rate. Telemetric recordings can provide a useful adjunct in intact animal studies.

It should be noted that while these models provide information that increases or decreases the understanding of the spectrum of drug effect, none will provide complete security with regard to drug effects in human subjects. In view of this, no single defined standardised or uniform method for preclinical screening of the effects of drug effects on cardiac repolarization could be identified from the literature or within this study's data packages reviewed. According to Zemzemi and colleagues (2013), none of the preclinical testing methods described has demonstrated a predictive value that makes it clearly superior to others. *In vivo* methods introduce an intrinsic degree of variability and need for QT correction in relation to the heart rate. This may introduce an error of over or undercorrection depending on the equation used and the species.

In vivo methods explore the potential effects of not only the parent compound but also of active metabolites, the exception being metabolites unique to man which must be studied in their own right *in vivo* and *in vitro* (Zemzemi et al, 2013). The value of post-marketing real world data gains importance here since even the most comprehensive preclinical testing strategy may not reveal discreet drug-related effects.

1.9 Regulatory implications

In the previous section, the various testing strategies deployed by the pharmceutical industry when testing there drugs was reviewed, however it was not until the 1990s, that the European Medicines Agency (EMA) and the US Food and Drug Agency (FDA) began the

move toward routine preclinical and clinical testing to determine whether drugs have the potential to cause QT prolongation (Shah, 2005). Figure 1.5 depicts the regulatory evolution of preclinical testing strategy guidance, leading to the release of ICH E14 guidance to industry as well as the discovery of QT shortening on a timeline created for this study.

In 1997, the EMA released a 'Points for Consideration' document addressed at the pharmaceutical industry and regulators to encourage the move toward a robust preclinical testing strategy. Health Canada and the FDA also released concept papers on the matter, until in 2005, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brought together the regulatory authorities and pharmaceutical industry to discuss the scientific and technical aspects of drug registration in relation to QT prolongation.

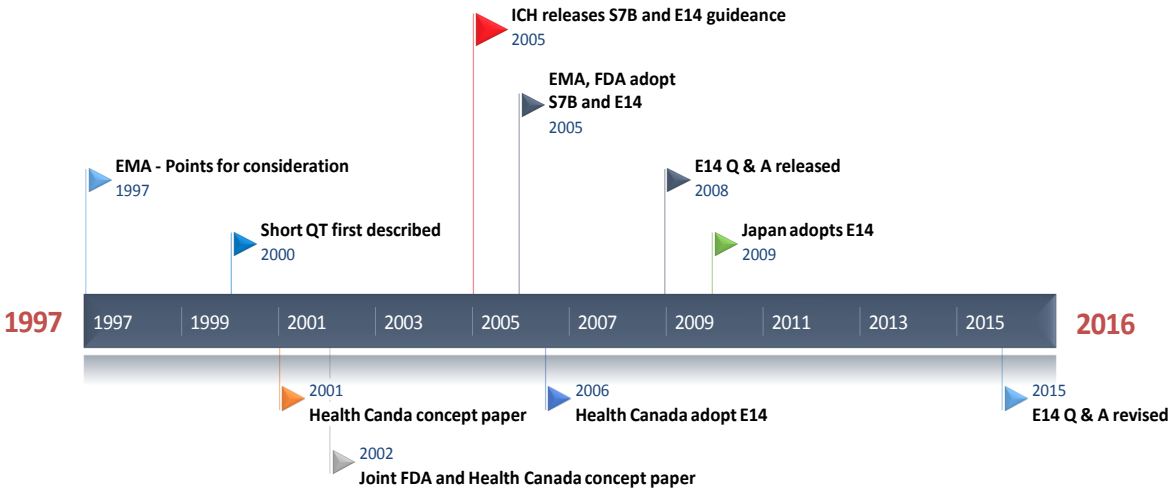


Figure 1.5 World-wide regulatory evolution of preclinical testing strategy guidance, culminating in release of ICH E14 guidance to industry.

In 2005, ICH S7B and E14 were released and laid out the preclinical testing strategy necessary for new chemical entities. With respect to QT shortening, no such guidance exists. This lack of guidance for the industry was a driving force for this study, since if QT interval shortening could be picked up as a signal from post-marketing data, more effort for its detection in the preclinical setting could be warranted.

1.9.1 Post-marketing requirements

New drugs are approved with a patient exposure average of 1 to 2 thousand patients, and are studied for short periods of time (Carlsson et al, 1990; Freeman et al, 2008). A drug may have an excellent safety profile in a few thousand patients but when administered to several million patients, rare toxicities may emerge. European legislation requires the reporting of adverse events in the form of spontaneous reporting[4]. These reports are collected from patients, health care providers, health authorities, medical literature, and other sources. The information is then entered by pharmaceutical companies or regulatory agencies into a central database, Eudravigilance (Appendix 1) for the cumulative adverse event data to be analyzed for potential safety signals. Although useful, spontaneous reports have some limitations (section 4.8).

[4] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. . 31/12/2010

1.9.2 Labelling implications

The labelling implications for a drug that changes the QT interval are considerable (Shah, 2002). Detailed consideration of safety, quality and efficacy enable a final decision to be made regarding the approvability of a new medicinal product, and where appropriate, the conditions for clinical use to be included in the SPC. These conditions for use have an impact on dosage schedules (maximum unit and daily doses), dose titration schedules, contraindications in terms of concurrent drugs and concurrent diseases, special warnings and precautions for use (special populations and monitoring and/or follow-up requirements), detailed descriptions of pharmacokinetic and pharmacodynamic interactions, listings of undesirable effects consequent to prolongation of QT interval, and means for monitoring and managing patients who experience an overdose of the drug (Redfern et al, 2003).

1.10 Aim and objectives of the study

The aim of this study was to detect signals of QT change with medicinal products, with the objective of:

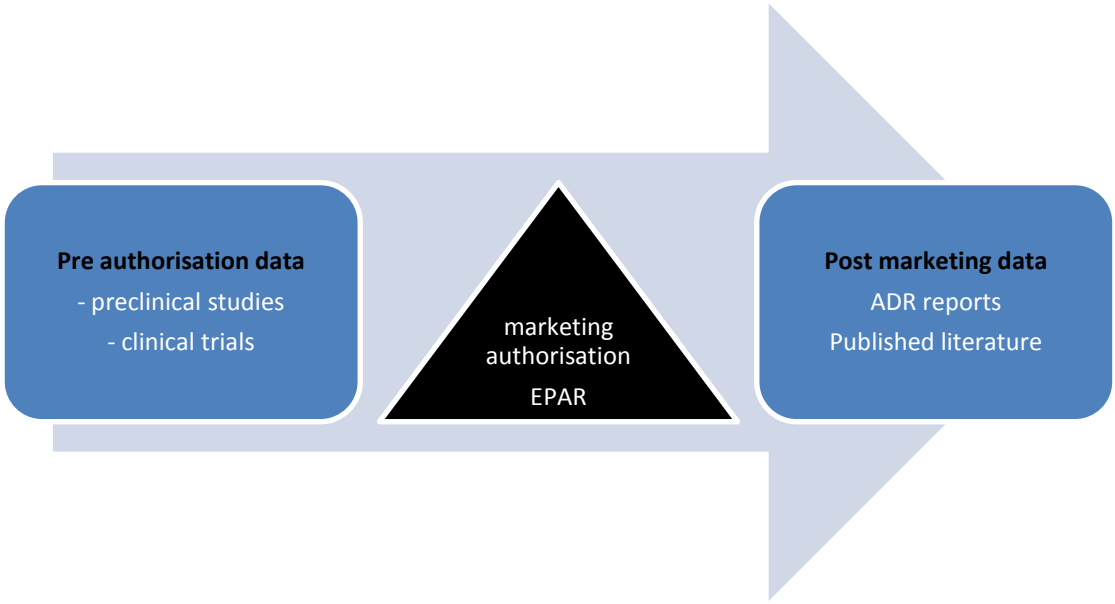
1. Analysing all data to determine whether the signals identified are true associations
2. Determining whether the risk of QT interval change is well reflected in the product information of medicinal products and if not, recommend changes to it
3. Creating a list of QT change frequency, for those products where QT change is an expected adverse event in the product information

4. Raising any signals assessed to be true associations, to the European regulatory agencies

Chapter 2: Methodology

2.1 Date sources

To achieve the aim, post-marketing ADR reports within a database were used to generate statistical signals of disproportionality between medicinal products and QT interval change. (study 1). If criteria were met for a medicinal product to be included, a full evaluation was performed using pre and postmarketing data (study 2). Figure 2.1 was created for this study to show how data is generated within the lifecycle of a medicinal product.



Preclinical and clinical testing forms the pre authoristion body of data. A marketing authorization is then sought based on conclusions of a positive benefit risk. These conclusions are published in the European Public Assessment Report (EPAR). Following placing of the medicinal product on the market, healthcare professionals and patients report their real world experience of use of the product by submitting ADR reports or publishing case reports in scientific journals.

Figure 2.1 Life-cycle data generation on a medicinal product

The data sources used were:

- ADR reports in Eudravigilance
- Scientific literature in PubMed
- Preclinical and clinical trials data within drug dossiers
- European Medicines Agency website Public Assessment Reports (EPAR)

2.1.1 Permission for access to dossiers and ADR reports

Approval to access dossier data was granted by the Malta Medicines Authority (MMA). For ADR reports, data was provided in aggregate, devoid of any patient or reporter identifiers. For drug dossiers, the data provided was in line with Heads of Medicines Agency/European Medicines Agency Guidance document on transparency and the release of commercially sensitive information or personal protected data after the granting of a marketing authorization[5]. The dossier parts involving commercially sensitive information on the manufacture and synthesis of the active substance were not provided. Personal data, relating to experts or designated personnel, or relating to patients in clinical trial study reports, was also not included. Preclinical and clinical development modules of the medicinal product dossier and their subsequent assessment by Competent Authorities, is not deemed to be commercially confidential, hence this data was provided.

[5] Heads of Medicines Agencies/European Medicines Agency guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (ma) application - release of information after the granting of a marketing authorization . 2012 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf

2.1.2 Permission to use the Bradford Hill criteria

Permission to use the Sir Austin Bradford Hill *The Environment and Disease: Association or Causation?* from Proceedings of the Royal Society of Medicine for this dissertation, was granted by SAGE Ltd (Hill, 1963), (Appendix 1). A definitive description of the Bradford Hill criteria can be found in the published paper (Hill, 1965) and in Appendix 1. These criteria for attributing disease causation to environmental factors have been used widely in epidemiology since their release in 1965 but were first acknowledged as applicable to pharmacovigilance and pharmacoepidemiology by Shakir and Layton in 2002 when they published a paper entitled 'Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria'. The criteria were then used by Perrio and colleagues to determine the causality of cisapride-induced arrhythmia hence demonstrating the validity of the Bradford Hill criteria as a framework for assessing causality (Perrio et al, 2007).

2.2 Study 1: Using ADR reports in Eudravigilance for signals of disproportionate reporting

The Eudravigilance database, was used to retrieve reports of QT prolongation reported between 1st of January 2004 to 31st August 2016. The parameters set, were to find which medicinal products have been reported to cause QT prolongation, and have a Proportional Reporting Ratio (PRR) of 1 or greater, and have at least 3 reported ADR cases. The same was done to retrieve denominator data for QT shortening and the same method was applied

for detecting signals of QT shortening with the two terms used interchangeably in this chapter.

2.2.1 Proportional Reporting Ratio calculations

The PRR method was used to infer disproportionate reporting by calculating the total number of reports for the drug as a denominator and the proportion of all reactions from ones of interest (reports on QT prolongation with drug Y versus all other reports on drug Y). The PRR calculations were made using the Eudravigilance Data Analysis Software (EVDAS) and by using two by two tables, as per Table 2.1 (Egberts et al, 2002).

Table 2.1 Signal detection two by two table

	Event of interest	**All other events**	**Total**
Product of interest	A	B	A+B
All other products	C	D	C+D
Total	A+C	B+D	A+B+C+D

Reproduced from:

Egberts AC et al. Use of measures of disproportionality in pharmacovigilance: three Dutch examples. Drug Saf 2002;25(6):453-458.

In the table above, A is the event of interest for the product of interest. B is all other events with the product of interest. C is the event of interest in all other products. D is all other events in all other products. An example of such a calculation is given in Table 2.2 below adopted from Evans et al, (2001).

Table 2.2 Example of a PRR calculation-rifabutin and uveitis

	Rifabutin	All other drugs
Uveitis	41	754
All other ADRs	14	591 958
TOTAL	55	592 712

PRR = 41/55 divided by 754/592, 712 = 586.
Chi-squared (1 df) = 22 740.

Reproduced from:

Evans SJ et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidem Drug Safe 2001 10/01;10(6):483-486

The expected value for a PRR is one (similar to the epidemiological concept of a relative risk of one) and the values generated are measures related to strength of association; the higher the PRR, the greater the strength of the signal. If a PRR is less than 1 it means that there are less reports than expected for that drug and event pair (Gogolak, 2003).

2.3 Criteria for Signal Evaluation: Expectedness

Once a series of signals with PRR greater than 1 were identified, these were checked for expectedness by reviewing the Summary of Product Characteristics (SPC) of the medicinal products in question. This was done since (1) the database does not distinguish between already labeled adverse events and (2) healthcare professionals report ADRs even if they are already known events and are listed in the SPC. The check for expectedness involved a thorough review of sections 4.3, 4.4, 4.5 and 4.8 on the contraindications, special warnings

and precautions for use, drug-drug interactions and undesired effects. Sections 5.1, 5.2 and on pharmacodynamics and pharmacokinetics of the product were also reviewed.

The expected signals identified were utilised to yield and compare specific risks of QT interval changes according to expected frequencies in the SPC (Table 6). Anatomical and Therapeutic Classification (ATC) codes were used to identify which therapeutic classes were expected to cause QT prolongation (Figure 10 section 3.1.3).

If the ADR was not listed in the SPC of the product, the product was carried forward to study 2. The clinical significance of the detected signals, their previous awareness, the biological and temporal plausibility and any relevant sources of information supporting the association were taken into consideration within study 2. A flow chart for this process with the areas where results were expected is depicted in Figure 2.2.

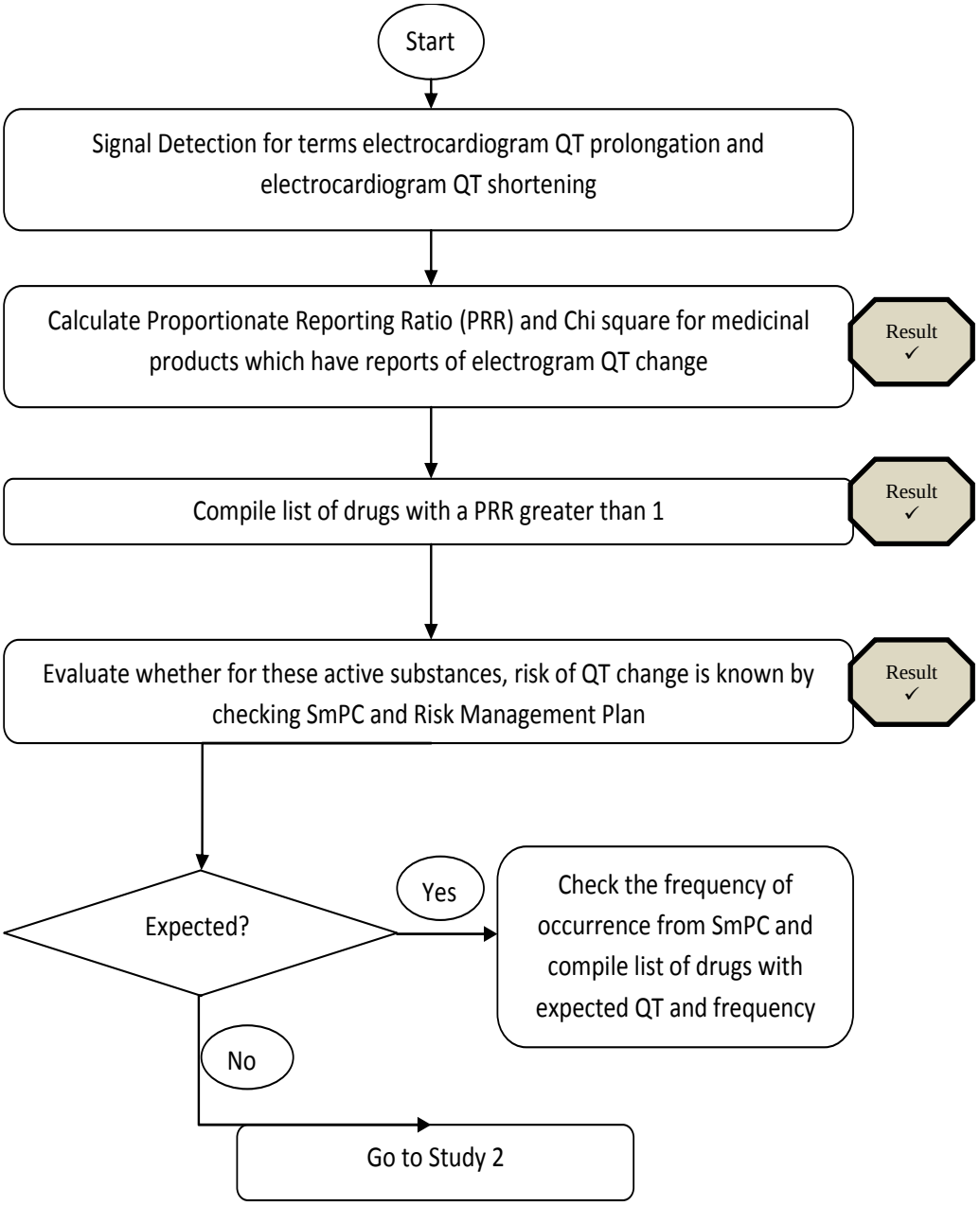


Figure 2.2 Process flow for study 1

2.4 Study 2: Signal assessment using the Bradford-Hill criteria

A flow chart of study 2 is presented as Figure 2.3. Full evaluations of previously unknown signals of QT prolongation or shortening were done using the Bradford Hill criteria. A detailed description of the Bradford Hill criteria is found in Appendix 1. Table 2.3 shows how the Bradford Hill criteria were applied to this study as a framework to guide the assessment process.

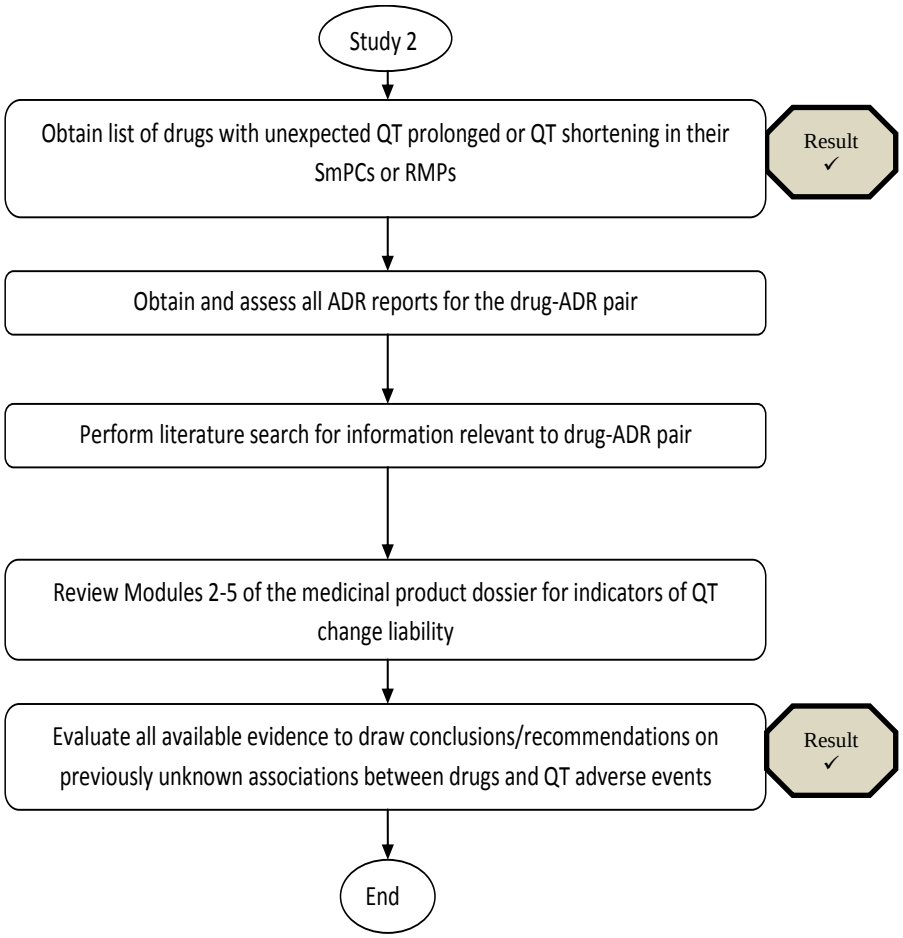


Figure 2.3 Process flow for study 2

Table 2.3 Bradford-Hill criteria as used for this study

Bradford Hill Criterion

1 Strength of association and coherence

Are there more reports of associations between the suspect drug and QT prolongation or TdP than would be expected by chance alone? Are there associations with palpitations, syncope sudden death or other events know to be associated with long/short QT

2 Biologically Plausible Mechanism

Does the suspect drug prolong QT or block the hERG channel or Ikr current in *in vitro* laboratory models?

3 Biological Gradient

Is there evidence of dose/concentration response in clinical and/laboratory data?

4 Experimental evidence and Temporality

Do clinical studies demonstrate that exposure to the suspect drug is followed by QT prolongation and/or TdP? Is there evidence of reversal with de-challenge?

5 Consistency

Do clinical studies show consistent results for QT prolongation and/or TdP

6 Specificity

Do clinical cases or studies report the usual associations with TdP (hypokalemia, bradycardia, drug-drug interactions) and lack evidence for alternative explanations (history of seizures, myocardial infarction)?

7 Analogy

Do chemically similar drugs have the ability to prolong QT and cause TdP?

Reproduced from:

Perrio M et al. Application of the bradford hill criteria to assess the causality of cisapride-induced arrhythmia: a model for assessing causal association in pharmacovigilance. Drug Saf 2007;30(4):333-346.

The data sources used were PRRs derived from ADR reports within the Eudravigilance database, preclinical and clinical trial data (section 2.4.2), the product information and available published literature for each medicinal product investigated (see chapter 3).

2.4.1 Data utilisation

2.4.1.1 *ADR reports*

Each of the ADRs reported were assessed to assign a causality score. Summaries of the ADR reports and their causality assessments are appended for each product. Data was downloaded from Eudravigilance in HTML form which is largely unstructured data, and hence substantial efforts in cleaning and summarising the data had to be deployed. ADRs are reported based on a suspicion of a healthcare professional or a patient that a drug caused an adverse event. When a single drug is given in a relatively healthy patient, and this patient experiences an ADR close to the time of administration, then assigning causality is easy and will most be seen as highly probably related to the drug. Many times it is not straightforward and therefore specific algorthims to standardise the method of causality assessments have been devised. This is helpful, since without such methods, there would be excessive subjectivity within the process.

2.4.1.2 *Causality assessment*

There is no universally accepted method for assessing causality of ADRs, however the most widely used is the French imputability method (Andrews & Mann, 2002) and was

used for this study. It is also the method of choice of the local national competent authority, the MMA. This method is described in the next section (section 2.4.1.3).

2.4.1.3 *The French imputability method*

The basic principles of the French method for assessing causality are described in Andrews & Mann and can be found within Appendix 1.

The scores assigned to the ADR cases were:

Highly probable	When a clinical event occurring in a plausible time relative to drug administration and which cannot be explained by concurrent disease The response to withdrawal of the drug (dechallenge) should be clinically plausible, with a satisfactory rechallenge procedure
Probable	Is a clinical event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease, and which follows a clinically reasonable response on withdrawal (dechallenge)
Possible	A clinical event, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease. Information on drug withdrawal may be lacking or unclear
Uncertain	A clinical event with a temporal relationship to the drugs administration in which other explanations and confounding factors make attribution to the drug doubtful however the association cannot be excluded
Unlikely:	A clinical event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which underlying disease or other drugs provide more plausible explanations

2.4.2 Dossier data

For those medicinal products carried forward to study 2, dossiers were accessed through a request for data from the MMA. The drug dossier is a collection of documents grouped together to describe all the technical aspects of a medicinal product and forms the basis for a marketing authorisation. The dossier is organised into five modules (Figure 2.4). Module 1 is specific to the region it is being submitted to, and Modules 2, 3, 4 and 5 are common for all regions.

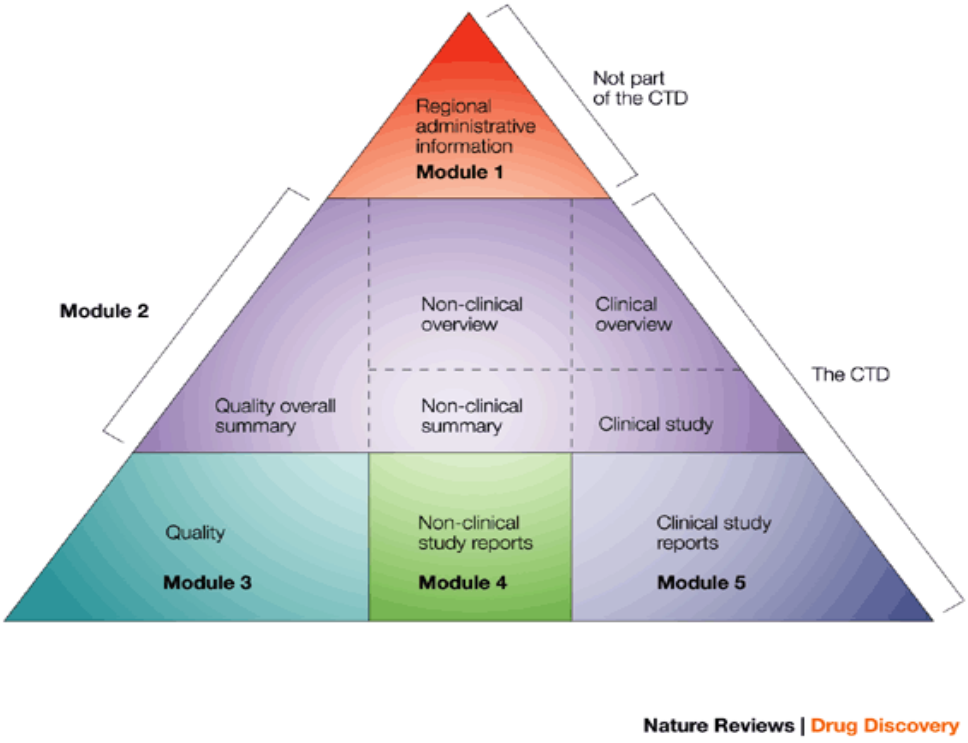


Figure 2.4 A medicinal products full dossier, showing module 1 and modules 2-5.

Reproduced from:

Molzon J. The Common Technical Document: the changing face of the New Drug Application; Nature Reviews Drug Discovery, 2003, 2:1:17.

The results of preclinical studies required by guidelines ICH S7B and E14 were downloaded from modules 2 and 4, and clinical studies with safety end points were obtained from modules 2 and 5. The data from preclinical and clinical studies was summarised by the researcher and commented upon in terms of interpretation for the research question.

2.4.3 Literature data

Articles in the US National Library of Medicine database (MEDLINE®) were retrieved using the PubMed tool for the time frame 1st January 2000 to 26th October 2016. The following search terms, together with the name of the active substance in question were used. The search criteria below can be inserted into PubMed to replicate the search, together with the name of the medicinal product in question.

("drug induced qt interval"[Title] OR "drug induced qt interval changes"[Title] OR "drug induced qt interval lengthening"[Title] OR "drug induced qt interval prolongation"[Title] OR "drug induced qt interval shortening"[Title] OR "drug induced qt prolongation"[Title] OR "drug induced qtc interval"[Title] OR "drug induced qtc interval prolongation"[Title] OR "drug induced qtc prolongation"[Title]))) AND *("2000/01/01"[Date - Publication]: "2016/10/26"[Date - Publication])*

In some instances, wider search terms were used, for example, in the case of the proton pump inhibitor pantoprazole when the signal required divergence from QT prolongation to hypokalaemia.

2.5 Dissemination of assessment results to the EU network

The signal assessment reports for asenapine and mirabegron (appendix 2 and 3) were sent to the EMA through the MMA. Following notification of the signal to the MMA, the assessment report was sent to the Director for post-licensing activities for peer review. The findings were also presented to the Medicines Review Committee (MRC) for any comments. This committee within the MMA meets to discuss regulatory and technical issues relating to ongoing medicinal product applications and post-authorisation activities as well as clinical trial applications with the objective of reaching an integrated opinion and position to be taken by the MMA.

The signal assessment report was then sent to the EMA through the European Pharmacovigilance Issues Tracking Tool (EPITT); a web-based system that is used by the EU network to track and monitor the safety of medicinal products. In the 'New Signals' section of this tool, there are designated fields, to populate with information such as the PRR, the most compelling case reports and other information. The proposed regulatory action is also specified therein. Through this system, the EMA gives its position on any signals raised, and decides whether the issue requires discussion at the next monthly plenary.

Chapter 3: Results

3.1 Study 1: Signal detection

3.1.1 QT prolongation

Results of the signal detection exercise for the term *QT prolongation*, retrieved 11,304 ADR reports from 404 different active substances. The 404 substances included both centrally authorised products (CAPs) (products having a single marketing authorisation applicable for all the EU) and nationally authorised products (products authorised in 1 or more EU countries through multiple authorisation procedures). A review of the 404 substances showed that some products are national products, that is, products available in one member state only. When using such databases signal prioritisation is important since the review/assessment of a signal is a lengthy process. In deciding whether to include products which were nationally authorised, it was noticed that many of these products were not authorised to be placed on the Maltese market (157/404) and to complete assessments for all the national products was not feasible within the time frame for this study. An approach to focus on the CAPs was taken, since this is more relevant at an EU level and for Malta.

Sixty-three of the 404 products were CAPs and were responsible for 20% of all the prolonged QT cases retrieved (n=2,234). Unlike the NAPs, the CAPs have common technical dossiers available online within an electoric portal which are accessible to the regulator. For the CAPs involved, the PRR statistical method was used to obtain PRRs with confidence intervals for each active substance. Tables 3.1 and 3.3 show the active substances that were hits from the electronic database and their PRRs in descending order.

These products were checked for whether QT interval prolongation was an expected adverse event in the product information.

3.1.2 Excluded products

Out of the 63 CAP products with PRR greater than 1, 20 were excluded. For 6 products, this was due to withdrawal in the EU market (dofetilide, nelfinavir, milnacipran, sumatriptan, tegaserod, apomorphine). An additional 4 products had no electronic dossiere submitted to the electronic portal by the respective marketing authorization holder (bupropion, buprenorphine, ritonavir, abacavir). Three products had full electronic dossiers but no post-marketing cases relevant to the CAP within the Eudravigilance database (lidocaine/prilocaine combination spray for premature ejaculation, midazolam paediatric oromucosal solution for single home use in status epilepticus, propranolol suspension for proliferating infantile haemangioma), while for febuxostat, emtricitabine, etravirine, memantine, lamivudine, caffeine and micafungin the centralized product was a generic and there was insufficient preclinical data within the drug dossier.

3.1.3 Expectedness

Of the 43 remaining products 33 were expected to cause QT prolongation according to their product information, (Table 3.2). These medicines have varying levels of risk of causing this ADR which is reflected in the SPC wording. Dextrometorphan, telithromycin, vandetanib, dronedarone, lopinavir, ritonavir combination and darunavir have a contraindication for use with other QT prolonging drugs. Arsenic, requires continuous ECG

monitoring while pasireotide, bedaquinile, nilotinib, crizotinib, dabrafenib, bozutinib require an ECG at baseline and at regular intervals following treament. With some treatments, instructions to cease therapy immediatly if QTc exceeds a defined threshold and to seek the advice of a cardiologist for the non-cardiac drugs is in place in the SPC, or to adjust posology, according to the level of QT change observed

From the drugs expected to cause QT prolongation, the majority were Antineoplastics (8) > followed by Antibacterials/Antifungals (5), Cardiac Therapy (4) > Antivirals (3) Psycholeptics (2) > Antiemetics (2) Urologicals (1) Antihistamines (1) Immunosuppresnats (1) Psychoanaleptics (1) Calcium homeostasis (1) Other nervous system (1) Pituitary and hypothalamic hormones and analogues (1) Drugs used for bone disease (1) and Contrast media (1) (Figure 3.1).

3.1.4 QT shortening

Results of the signal detection exercise for the term *QT shortening*, retrieved 69 ADR reports from 13 different active substances (see Table 3.3). Again, the CAPs were selected meaning that 2 products with 9 cases were available for review. These 2 products were olanzapine and fingolimod.

Table 3. 1 Signal detection results for electrocardiogram QT prolonged (n=63)

Scientific Composition (High Level)	PT*	PRR (-)	**PRR***	PRR (+)	CHI^2 PRR Analysis -
BEDAQUILINE	Electrocardiogram QT prolonged	33.307948	**73.4967745**	162.17679	358.293052
VANDETANIB	Electrocardiogram QT prolonged	53.425519	**67.2141673**	84.561543	3966.97434
ARSENIC	Electrocardiogram QT prolonged	53.636175	**64.2498211**	76.963719	6185.70075
DOFETILIDE	Electrocardiogram QT prolonged	32.210569	**44.668982**	61.946063	1365.60424
PASIREOTIDE	Electrocardiogram QT prolonged	8.3606017	**17.2583658**	35.625569	107.416917
NILOTINIB	Electrocardiogram QT prolonged	14.272952	**16.1060221**	18.174512	3592.46164
TELAVANCIN	Electrocardiogram QT prolonged	4.2508054	**12.9392847**	39.386675	33.1242188
DRONEDARONE	Electrocardiogram QT prolonged	10.611061	**12.7141662**	15.234106	1231.34214
PALONOSETRON	Electrocardiogram QT prolonged	4.8437102	**10.0671156**	20.923386	57.2732488
RANOLAZINE	Electrocardiogram QT prolonged	6.0475689	**8.3978215**	11.661447	227.94258
IVABRADINE	Electrocardiogram QT prolonged	5.5801972	**7.4820757**	10.032165	246.728674

*PT: Preferred Term, PRR: Proportional Reporting Ratio (-/+)negative and positive confidence intervals

…Continued

Scientific Composition (High Level)	PT*	PRR (-)	PRR*	PRR (+)	CHI^2 PRR Analysis -
CRIZOTINIB	Electrocardiogram QT prolonged	4.3559567	**6.02708619**	8.3393318	150.83587
REGADENOSON	Electrocardiogram QT prolonged	2.2221484	**5.87888251**	15.553083	16.2309746
LOXAPINE	Electrocardiogram QT prolonged	3.1042688	**5.22516597**	8.7951015	47.8916988
DEXMEDETOMIDINE	Electrocardiogram QT prolonged	2.6662694	**4.93771279**	9.14424	31.4531835
ASENAPINE	Electrocardiogram QT prolonged	3.2892979	**4.85843878**	7.1761293	76.6262426
NELFINAVIR	Electrocardiogram QT prolonged	2.486187	**4.60541586**	8.5310779	28.2711997
OLANZAPINE	Electrocardiogram QT prolonged	4.065869	**4.54358021**	5.0774192	853.064726
PRUCALOPRIDE	Electrocardiogram QT prolonged	1.4633894	**4.5089675**	13.892945	8.21071318
DESLORATADINE	Electrocardiogram QT prolonged	2.3798994	**3.87682744**	6.3153052	34.1929885
VORICONAZOLE	Electrocardiogram QT prolonged	3.0473171	**3.7981787**	4.7340533	162.098176
PROPRANOLOL	Electrocardiogram QT prolonged	2.6847853	**3.71831998**	5.149724	71.4881019
TELITHROMYCIN	Electrocardiogram QT prolonged	1.9917484	**3.29801756**	5.460991	24.046414

*PT: Preferred Term, PRR:Proportional Reporting Ratio (-/+) negative and positive confidence intervals

…Continued

Scientific Composition (High Level)	PT*	PRR (-)	PRR*	PRR (+)	CHI^2 PRR Analysis -
LEVOFLOXACIN	Electrocardiogram QT prolonged	2.7851443	**3.18405407**	3.6400988	319.503821
FINGOLIMOD	Electrocardiogram QT prolonged	2.5130766	**3.0971149**	3.8168836	124.276326
ATAZANAVIR	Electrocardiogram QT prolonged	2.0467428	**3.00307308**	4.406244	34.7434238
PALIPERIDONE	Electrocardiogram QT prolonged	2.3086967	**2.98546899**	3.8606307	76.3745915
MEMANTINE	Electrocardiogram QT prolonged	1.9670799	**2.95690085**	4.4447928	29.8001628
BUPROPION	Electrocardiogram QT prolonged	2.3216724	**2.87905505**	3.5702531	101.280087
MIDAZOLAM	Electrocardiogram QT prolonged	1.8814106	**2.57387336**	3.5212006	37.4951754
AGOMELATINE	Electrocardiogram QT prolonged	1.7456826	**2.51038585**	3.6100704	26.3503592
MILNACIPRAN	Electrocardiogram QT prolonged	1.308466	**2.51025973**	4.8158714	8.19160285
DASATINIB	Electrocardiogram QT prolonged	1.8279599	**2.49102666**	3.3946116	35.6591776
BOSUTINIB	Electrocardiogram QT prolonged	0.7974867	**2.46440551**	7.6155431	2.61643429
RITONAVIR	Electrocardiogram QT prolonged	1.7118537	**2.41936861**	3.4193017	26.6362527

*PT: Preferred Term, PRR:Proportional Reporting Ratio (-/+) negative and positive confidence intervals

…Continued

Scientific Composition (High Level)	PT*	PRR (-)	PRR*	PRR (+)	CHI^2 PRR Analysis -
DARUNAVIR	Electrocardiogram QT prolonged	1.3894012	**2.34313444**	3.9515432	10.7923134
EMTRICITABINE	Electrocardiogram QT prolonged	0.7025901	**2.17206238**	6.7149463	1.90164065
GADOVERSETAMIDE	Electrocardiogram QT prolonged	0.6742018	**2.08456029**	6.4452391	1.6966499
GLYCOPYRRONIUM	Electrocardiogram QT prolonged	0.5884042	**1.81997149**	5.629287	1.11079065
ETRAVIRINE	Electrocardiogram QT prolonged	0.6821481	**1.81380443**	4.8228334	1.46368729
DEGARELIX	Electrocardiogram QT prolonged	0.5839277	**1.80616084**	5.58668	1.08189788
LOPINAVIR, RITONAVIR	Electrocardiogram QT prolonged	0.9740837	**1.64348803**	2.7729166	3.5317275
LIDOCAINE,PRILOCAINE	Electrocardiogram QT prolonged	1.0887189	**1.63766693**	2.4634026	5.71320713
DENOSUMAB	Electrocardiogram QT prolonged	1.2715032	**1.61881105**	2.0609852	15.5580261
VARDENAFIL	Electrocardiogram QT prolonged	0.5990967	**1.59340863**	4.2379652	0.8858888
SUMATRIPTAN	Electrocardiogram QT prolonged	0.8405154	**1.47892527**	2.6022367	1.86377756
TEGASEROD	Electrocardiogram QT prolonged	0.6896868	**1.44509834**	3.0279094	0.96146419

*PT: Preferred Term, PRR:Proportional Reporting Ratio (-/+) negative and positive confidence intervals

…Continued

Scientific Composition (High Level)	PT*	PRR (-)	**PRR***	PRR (+)	CHI^2 PRR Analysis -
ABACAVIR	Electrocardiogram QT prolonged	0.6396681	**1.42211191**	3.1616432	0.75323867
CAFFEINE	Electrocardiogram QT prolonged	0.5241953	**1.39453735**	3.7099426	0.44745024
CINACALCET	Electrocardiogram QT prolonged	0.6857678	**1.36998835**	2.7368857	0.80081161
MICAFUNGIN	Electrocardiogram QT prolonged	0.5085241	**1.35291629**	3.5994018	0.36903805
LEVETIRACETAM	Electrocardiogram QT prolonged	0.9905692	**1.33576228**	1.8012481	3.62412738
BUPRENORPHINE	Electrocardiogram QT prolonged	0.8897995	**1.31657632**	1.9480492	1.90353927
DABRAFENIB	Electrocardiogram QT prolonged	0.4099025	**1.268853**	3.9277335	0.17128438
RIVASTIGMINE	Electrocardiogram QT prolonged	0.8736792	**1.26521595**	1.8322187	1.55662972
GRANISETRON	Electrocardiogram QT prolonged	0.4077248	**1.26212382**	3.9069408	0.16368553
MIRABEGRON	Electrocardiogram QT prolonged	0.637196	**1.22374201**	2.3502102	0.36879877
APOMORPHINE	Electrocardiogram QT prolonged	0.3927026	**1.21570272**	3.7634925	0.11507558
DEXTROMETHORPHAN,QUINIDINE	Electrocardiogram QT prolonged	0.6399515	**1.18862267**	2.2077045	0.29981

* PT: Preferred Term, PRR:Proportional Reporting Ratio (-/+) negative and positive confidence intervals confidence intervals

…Continued

Scientific Composition (High Level)	PT*	PRR (-)	**PRR***	PRR (+)	CHI^2 PRR Analysis -
LAMIVUDINE	Electrocardiogram QT prolonged	0.6100343	**1.05018484**	1.8079119	0.03121813
LACOSAMIDE	Electrocardiogram QT prolonged	0.510495	**1.02015009**	2.0386216	0.00318978
PANTOPRAZOLE	Electrocardiogram QT prolonged	0.6910305	**1.0076424**	1.4693174	0.00156513
FEBUXOSTAT	Electrocardiogram QT prolonged	0.3766168	**1.00241448**	2.6680559	2.3313E-05

Table 3.2 Medicines expected to cause QT prolongation as per product information, frequency, ATC code and therapeutic class (n=33).

	Drug List	Frequency*	ATC code	Therapeutic Class
1	Vandetanib	very common	L01XE	Antineoplastic agents
2	Bedaquiline	common	J04AK05	Antimycobacterials
3	Pasireotide	common	H01CB05	Pituitary and hypothalamic hormones and analogues
4	Nilotinib	common	L01XE08	Antineoplastic agents
5	Crizotinib	common	L01XE16	Antineoplastic agents
6	Regadenoson	common	C01EB21	Cardiac Therapy
7	Paliperidone	common	N05AX13	Psycholeptics
8	Bosutinib	common	L01XE14	Antineoplastic agents
9	Telavancin	uncommon	J01XA03	Antibacterials for systemic use
10	Olanzapine	uncommon	N05AH03	Psycholeptics
11	Voriconazole	uncommon	J02AC03	Antimycotics for systemic use
12	Dasatinib	uncommon	L01XE06	Antineoplastic agents
13	Degarelix	uncommon	L02BX02	Antineoplastic endocrine therapy
14	Dextromethorphan, Quinidine	uncommon	N07XX59	Other nervous system drugs
15	Palonosetron	uncommon	A04AA05	Antiemetics and antinauseants
16	Darunavir	uncommon	J05AE10	Antivirals for systemic use
17	Atazanavir	rare	J05AE08	Antivirals for systemic use
18	Denosumab	rare	M05BX04	Drugs for bone disease
19	Gadoversetamide	very rare	V08CA06	Contrast media
20	Telithromycin	unknown	J01FA15	Antibacterials for systemic use
21	Rivastigmine	unknown	N06DA03	Psycoanalepti
22	Cinacalcet	unknown	H05BX01	Calcium homeostasis

…Continued

23	Dabrafenib	unknown	L01XE23	Antineoplastic agents
24	Arsenic	unknown	L01XX27	Antineoplastic agents
25	Dronedarone	unknown	C01BD07	Cardiac therapy
26	Levofloxacin	unknown	J01MA12	Antibacterials for systemic use
27	Fingolimod	unknown	L04AA27	Immunosuppresants
28	Ranolazine	unknown	C01EB18	Cardiac therapy
29	Ivabradine	unknown	C01EB17	Cardiac therapy
30	Lopinavir, ritonavir	unknown	J05AR10	Antivirals for systemic use
31	Desloratadine	unknown	R06AX27	Antihistamines for systemic use
32	Vardenafil	unknown	G04BE09	Urologicals
33	Granisetron	unknown	A04AA02	Antiemetics and antinauseants

Frequency categories defined as follows: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Frequency unknown (cannot be estimated from the available data)

Table 3.3 Signal detection results for electrocardiogram QT shortened (n=13)

Scientific Composition	Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2
ATENOLOL	Electrocardiogram QT shortened	15.46894923	**38.09899164**	93.83527878	170.7050773
CALCIUM CARBONATE	Electrocardiogram QT shortened	29.09024392	**91.84951222**	290.0055744	260.6990964
CARBAMAZEPINE	Electrocardiogram QT shortened	2.729507831	**7.43596404**	20.25770382	21.30278746
CLOZAPINE	Electrocardiogram QT shortened	6.33920789	**12.226945**	23.58310163	91.76086603
DIGOXIN	Electrocardiogram QT shortened	51.16638235	**93.86998277**	172.214123	957.1931514
FINGOLIMOD	Electrocardiogram QT shortened	4.332148271	**13.68978324**	43.26033028	34.12581374
IBUPROFEN	Electrocardiogram QT shortened	2.89463238	**7.885778438**	21.48303943	22.99365524
OLANZAPINE	Electrocardiogram QT shortened	3.688354725	**9.086285287**	22.38412151	34.00536645
PARACETAMOL	Electrocardiogram QT shortened	4.375376238	**9.459215328**	20.45007098	48.8820744
QUETIAPINE	Electrocardiogram QT shortened	2.193832914	**5.976711094**	16.28249593	15.84780411
RAMIPRIL	Electrocardiogram QT shortened	5.491384573	**17.35234119**	54.83202657	44.70673791
SIMVASTATIN	Electrocardiogram QT shortened	2.304484399	**7.282774097**	23.01547303	15.72451397
ZIPRASIDONE	Electrocardiogram QT shortened	3.753808474	**15.24089019**	61.87975107	26.02862325

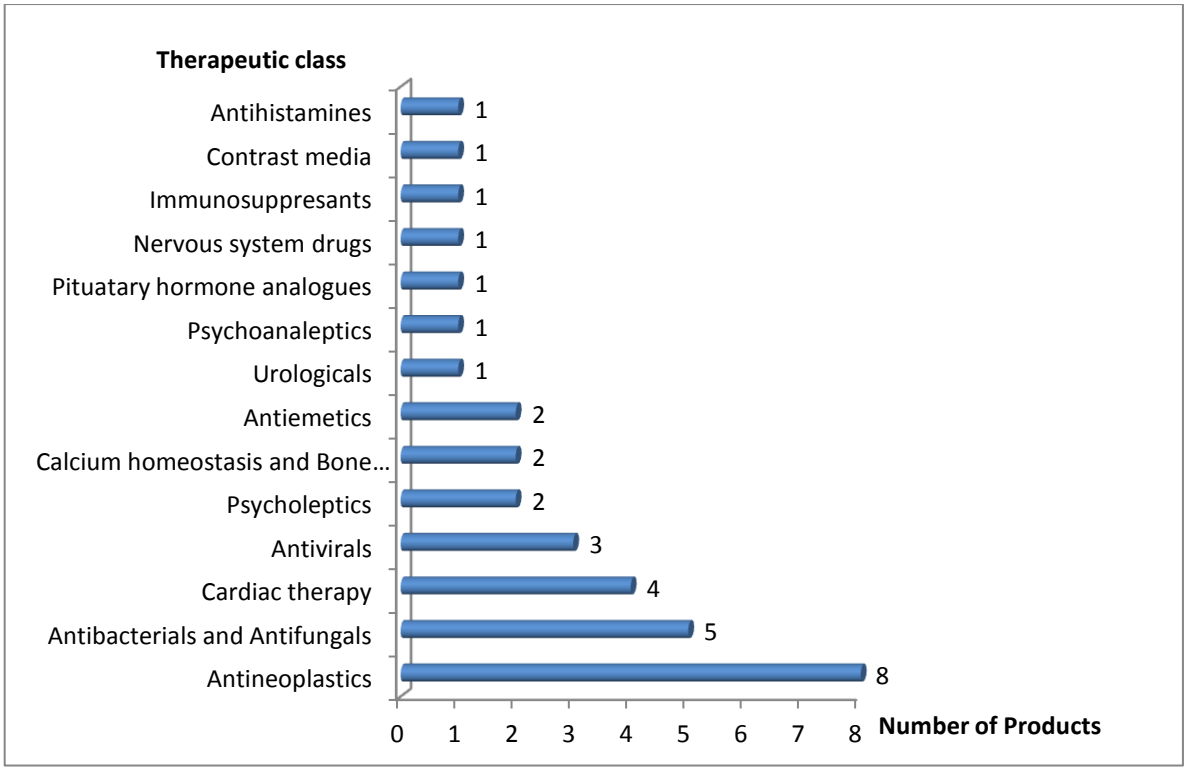


Figure 3.1 Therapeutic areas expected to cause QT prolongation in their product information (n=33)

3.1.5 Products assessed in study 2

Nine products were not expected to cause QT prolongation according to their product information (PI) and 1 product had conflicting information within the PI and so was also included for a full assessment.

Ten products were carried forward to study 2 to be fully assessed within the BH criteria. The products were agomelatine, asenapine, dexmedetomidine, glycopyrronium, loxapine, levetiracetam, lacosamide, mirabegron, prucalopride and pantoprazole. Asenapine had conflicting information in the SPC since it was listed in section 4.8 as an expected event but

in the warnings 4.4 section, the SPC states that clinically relevant QT interval prolongation is not expected

3.2 Study 2: Bradford Hill Assessments

Data from the different data sources was summarised and assessed for each of the 12 medicinal products as will be seen in the following sections. In the interest of maintaining an appropriate word count, the whole assessment report generated was not included within these results but provided as appendices 2-13 on CD-rom.

3.2.1 Investigations on Prolonged QT

3.2.1.1 Agomelatine: Valdoxan®

Formulations: 25 mg film-coated tablets

Mechanism of action: A new pharmacological mechanism of action, which combines melatonin MT1 and MT2 agonist properties, with a serotonin 5-HT2C antagonist effect.

Date EU approval: 19th February 2009

Indication: Treatment of major depressive episodes[6]

Availability in Malta: Available in the private sector, not on formulary list.

Current SPC wording: Does not mention QT prolongation in any section.

Bradford Hill criteria assessment

Strength of association

2.51 PRR, (PRR-1.75, PRR+ 3.61) 18 ADR reports

Biological plausibility

Agomelatine did not prolong QT or significantly block the hERG channel, in *in vitro* or *in vivo* laboratory models therefore a biological plausibility in terms of hERG effect is not apparent with agomelatine.

Biological gradient

Increased blockade of I_{Kr} at increased dose was not observed in company studies.

[6] Valdoxan 25 mg film-coated tablets EPAR-product information [internet] updated 2016 Jan 12; cited 2016 Sep 28. Available from http://www.ema.europa.eu

In post marketing data, very high doses of agomelatine in overdose did not lead to greater prolongation of the QT interval.

Experimental evidence and ADR reports

Two randomised, controlled through QT studies published in the literature (in healthy volunteers), did not show any evidence of QT prolongation. (Donazzolo et al 2014; Marx et al 2013). A signal report published in the WHO newsletter concluded that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose Herrera-Comoglio (2013).

Within the ADR reports 14 /18 cases were temporally related and a contribution of agomelatine to QT interval prolongation could not be excluded. From the 14 cases, 7 were judged as having a highly probable, probable or possible attribution to agomelatine while in the other 7 uncertain cases, the role of agomelatine could not be excluded.

Consistency

Both healthcare professionals and patients reported the same type of event. Reports originate from different countries in the EU and non EU with possibly different prescribing patters.

Specificity

Agomelatine was not found to bind hERG potassium channel. No plausible mechanism for QTc interval prolongation could be seen from preclinical data.

Analogy

Agomelatine has a novel mode of action which is markedly different from other antidepressants. No analogy can be drawn in this case.

Overall assessment:

In favour of the association, the most compelling evidence comes from 7/14 post marketing cases with highly probable, probable or possible score and the signal report of the WHO which concluded that agomelatine may prolong the QT interval in patients with predisposing risk factors or overdose. Against the association is the preclinical data as well as the 2 placebo controlled clinical trials in healthy volunteers which did not show any effects of QT prolongation by agomelatine. Based on this evidence, no change to the SPC was seen to be warranted.

3.2.1.2 Asenapine: Syncrest®

Formulations: 5 mg and 10 mg sublingual tablets

Mechanism of action: Not fully understood, however based on receptor pharmacology, it is proposed that efficacy is mediated mainly through antagonist activity at D2 and 5-HT2A receptors**.**

Date EU approval: 1st September 2010

Indication: Treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.[7]

Availability in MT: Not available

Current SPC wording:

Section	Wording
4.2 Contraindications	Not mentioned
4.4 Warnings	Clinically relevant QT prolongation does not appear to be associated with asenapine.
4.5 Interactions	Not mentioned
4.8 List of ADRs	Listed; frequency uncommon
5.0 Pharmacology	Not mentioned

Bradford Hill criteria assessment

Strength of association

4.60 PRR (PRR-3.29/ PRR+7.18), 17 ADR Case reports

Biological plausibility

In vitro studies in isolated rabbit and guinea-pig cardiac muscle and rabbit aortic tissue showed asenapine induced hERG blockade at very high doses.

[7] Sycrest 5 mg sublingual tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Aug 11; cited 2016 Sep 23. Available from http://www.ema.europa.eu

In vivo asenapine induced dose-dependent negative inotropic and positive chronotropic effects accompanied by QTc interval prolongation, orthostatic hypotension on tilt with marked tachycardia. Sublingually administered asenapine (as is currently authorised for use in the EU) had fewer cardiovascular effects however QTc prolongation was observed for both sublingual (not statistically significant) and oral formulations.

Biological gradient

Blockade of inward potassium current occurred only at the higher doses tested. Therefore a biological gradient is not apparent.

Experimental evidence and ADR reports:

In schizophrenia clinical trials the overall incidence of QT prolongation in asenapine treated subjects was comparable to that seen with placebo (in the short-term trials) and olanzapine (in the long-term trials) but no serious adverse events that are associated with QT prolongation were reported (sudden death, cardiac arrest, ventricular fibrillation, or TdP). In a company sponsored study in 148 schizophrenia patients using a novel testing method called the E-R test, no significant QT prolongation was observed (Chapel et al, 2009). When the E-R method was replaced by the ICH recommended intersection-union test (IUT) method QT prolongation was observed (Chapel et al, 2011). This latter study was conducted after the product had obtained a marketing authorization.

In terms of temporality of the post marketing cases, all the 16 assessed had a temporal relationship between the events and the initiation of treatment. In 2 cases asenapine was the only suspect drug and in 4 cases decreases in the dosage or stopping treatment with asenapine resolved the symptoms (positive dechallenge).

Consistency:

Both healthcare professionals and patients reported the same event. Reports originate from different countries in the EU and non EU with possibly different prescribing patters. 2 cases had the same profiles, ie. QT prolongation plus mouth ulcers (1 with causality probable and 1 uncertain case). Mouth ulcers are an expected adverse event with asenapine. Physicians and patients have reported the same event. Reports originate from different countries in EU and non EU with possibly different prescribing patters. Signal involves both healthy volunteers (experimental evidence) and post-marketing evidence.

Specificity:

In preclinical data asenapine was found to bind to and block hERG and affect the action potential (AP) duration which provides a plausible mechanism for QTc interval prolongation

Analogy:

Other antipsychotics bind to hERG, which provides an analogy for asenapine causing clinically relevant QTc interval prolongation.

Overall assessment:

In the Eudravigilance database the association between asenapine and QT interval prolongation was disproportionally reported for this drug over others with a strong PRR value. Literature and case review supports the relation, and preclinical data demonstrates a mechanism of action. While this event is already listed in section 4.8 with a frequency uncommon, a conflicting statement in 4.4 exists where it is stated that clinically relevant QT prolongation is not expected with this product. The post marketing cases reviewed show that a clinically relevant QT prolonging effect is occurring. The proposal therefore is to remove the statement ‘clinically

relevant QT prolongation is not expected with asenapine' from the 4.4 wording (warnings section) from the SPC. This proposal was sent to the European Medicines Agency's pharmacovigilance Rapporteur (United Kingdom) (see section 3.4 for response from the UK rapporteurs).

3.2.1.3 Dexmedetomidine: Dexdor®

Formulation: 100 ug/ml concentrate for solution for infusion

Mechanism of action: Dexmedetomidine is a selective alpha-2 receptor agonist with sympatholytic effects, through decrease of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem.

Date EU approval: 16th September 2011

Indication: For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3.[8]

Availability in MT: Not available

Currently SPC wording: QT prolongation is not mentioned in any section.

Bradford Hill criteria assessment

Strength of association

4.93 PRR (PRR-2.67/ PRR+ 9.14), 8 ADR reports

Biological plausibility

Overall dexmedetomidine and its major human metabolites showed limited hERG blocking activity in *in vitro* and *in vivo* studies. Moderate AP duration prolongation was evident in the dog Purkinje fiber assay at supratherapeutic dexmedetomidine concentrations but not in isolated rabbit heart preparation.

[8] Dexdor 100 micrograms/ml concentrate for solution for infusion EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Jun 09; cited 2017 Jan 26. Available from http://www.ema.europa.eu

Using the QT Sarma method for heart rate correction, dexmedetomidine showed prolongation of the QTc in dogs but the company states that the effect is most likely an indirect physiological effect induced by hypothermia. Therapeutic hypothermia is often used in ICU for preventing neurologic injury and, mild to moderate hypothermia (≥ 30○C), despite of an increase in QTc, is not known to increase risk for clinically significant arrhythmias.

Biological gradient

Increased QT interval prolongation was not seen with increasing doses of dexmedetomide studied *in vivo* or *in vitro*.

Experimental evidence and ADR reports:

Literature review revealed conflicting information. In a study by Gorges et al (2015), changes in QTc associated with a rapid bolus dose of dexmedetomidine (dex) were studied and it was found that a rapid bolus dose transiently shortened corrected QT intervals (Gorges et al, 2015). Kim et al (2016) studied the effect of dex on Heart Rate-Corrected QT Intervals in forty-seven patients. Here, dex also significantly shortened the QTc interval. The results by Kim were also confirmed by Cho et al (2016) in their study on the effects of dex on changes in heart rate and hemodynamics during tracheal intubation. Results showed that dex suppressed sympathetic hyperactivity and attenuated QTc prolongation during intubation. In contrast, a literature report by Shields in 2008 describes QT prolongation. In the patient described in this article, heart block occurred and the Q-Tc interval became prolonged after muscle relaxant reversal with neostigmine; both cases were considered to be related to the combination of agents used in the case, as well as to other predisposing factors such as morbid obesity. The agents used that affected cardiac conduction were neostigmine, desflurane, droperidol, dolasetron, and dexmedetomidine. (Shields, 2008)

Of the 8 postmarketing cases assessed, all had a temporal relationship between the events and the initiation of treatment. Some cases were confounded by other drugs and some occurred in the presence of underlying cardiac conditions or other confounders.

Consistency:

There is a level of inconsistency in the overall data for this drug especially from the literature search. Two published cases of clear QT prolongation and 3 studies suggesting that there could be a protective effect of dexmedotimidine on the QT interval.

Specificity:

In preclinical data dexmedetomidine and its metabolites were found to bind and block the hERG potassium channel only at massive doses however no effect was seen on the action potential duration.

Analogy:

No analogy can be drawn in this case

Overall assessment:

In the Eudravigilance database the association of dexmedotomide with QT prolongation was disproportionally reported for this drug over others. A mechanism of action is possible through hERG blockade however this occurred only at massive doses. Literature and case review show a divergent picture, and therefore do not support the relation.

3.2.1.4 Glycopyrronium: Seebri breezhaler®

Formulations: 44 micrograms inhalation powder, or 200 micrograms/ml Solution for Injection, 1 or 2mg tablets.

Indications: Inhaler: maintenance bronchodilator treatment of Chronic Obstructive Pulmonary Disease (COPD) [9] For the injectable form, it is used to (1). reverse residual neuromuscular blockade produced by muscle relaxants. (2) As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents. (3) As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of suxamethonium or due to cardiac vagal reflexes. [10] As tablets**:** For use in adults as add-on therapy in the treatment of peptic ulcer.[11]

Date of EU approval: 22nd June 2010

Availability in MT: Available on the Government Formulary List (injectible), private market (inhaler). Tablets are not available in MT.

Current SPC wording:

Section	Wording
4.3 Contraindications	Not listed
4.4 Warnings **(wording is present only for inhaler, not for injectible or tablets)**	Patients with a history of cardiovascular disease Patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc (Fridericia method) was prolonged (>450 ms for males or >470 ms for females) were excluded from the clinical trials, and therefore the experience in these patient groups is limited. Seebri Breezhaler should be used with caution in these patient groups.
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

[9] Seebri Breezhaler 44 micrograms inhalation powder, hard capsules EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Nov 22; cited 2017 Jan 12. Available from http://www.ema.europa.eu

[10] Accord Healthcare Limited. Summary of Product Characteristics Glycopyrronium Bromide 200 micrograms/ml Injection. Electronic Medicines Compendium 2016.

[11] MHRA Gycopyrronium bromide SmPC and Leaflet
http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1475212043510.pdf

Bradford Hill criteria assessment

Strength of association

1.82 PRR (PRR-0.59/ PRR+5.63), 3 ADR reports

Biological plausibility

Inhibition of the hERG current was only observed at concentrations significantly higher than the maximum human exposure (Cmax) at the recommended clinical dose. In *in vitro* studies, transient effects on heart rate and blood pressure were seen following an inhaled dose of 0.149 mg/kg (i.e., >100-fold the recommended clinical dose based on body surface area), transient increases in heart rate and transient decreases in heart rate-corrected QT intervals were observed.

Biological gradient

No increasing QT prolongation was seen with increasing doses of glycopyrronium.

Experimental evidence and ADR reports:

In a company QTc clinical study a single 400 µg dose (8 times the projected therapeutic dose of 50 µg) had no relevant effect on the corrected QTcF interval. Two studies by Drollmann also did not find the any effect on QT in young healthy volunteers (Drollmann et al 2014a; Drollmann et al 2014b)

In the literature, Pleym reports the case of a 27 year old woman with QT prolongation upon administration of glycopyronnium injection intraoperatively (Pleym et al, 1999), while Saarnivaara and Simola, 1998 describe patients who experiences QT prolongation when given anticholinesterase-anticholinergic combinations and warn that glycopyrronium should be avoided in patients having a long QT interval syndrome or a prolonged QT interval from other causes (Saarnivaara and Simola, 1998). In the post marketing adverse

event cases, temporal relationships were present in all cases but were not very suggestive except in one case. Confounding factors were present in all the cases. Dechallenge was positive in only 1 case.

Consistency:

Cases occurred with both the inhaler and the injectable preparation. However, all except for 1 causality assessment of post marketing data had outcome Uncertain.

Specificity:

Glycopyrronium is a high affinity muscarinic receptor antagonist with hERG activity at high doses.

Analogy:

Other anticholinergics are not known to prolong the QT interval.

Overall assessment:

In the Eudravigilance database the association was disproportionally reported for this drug over others. Preclinical data did not entirely support a mechanism of action. Literature and case review do not robustly support the relation. An inconsistency appears to be present between the product information of the injectibe and the inhaler, where in the inhaler SPC a warning against the use of glycopyrronium bromide in patients with LQTS is present in the inhaler but not in the injectible or tablets. Extending the warning present in the inhaler also to the injectible and tablets, makes sense considering that oral and injected glycopyrronium attains higher systemic dose levels when compared to the inhaler. However based on the data assessed here, it is not seen to be enough to support the change in SPC.

3.2.1.5 Lacosamide: Vimpat®

Formulations: Tablets (50 mg; 100 mg; 150 mg; 200 mg), syrup (10 mg/ml) and solution for infusion (10 mg/ml).

Mechanism of action: Not fully elucidated but has been shown to selectively enhance slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Date EU approval: 29th August 2008

Indication: As adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy

Availability in MT: Not available on government formulary list, available in private sector.

Current SPC wording: Not listed in any section

Bradford Hill criteria assessment

Strength of association

1.02 PRR (PRR-0.51/ PRR+2.04), 8 ADR reports

Biological plausibility

In vitro lacosamide reduced Na+ current in cardiac cells and affected action potential duration in cardiac tissue and sodium current in isolated cells, starting at concentrations which are achieved with the maximum human dose, ie 50 to 60 μmol/L. Effects on sodium current were dependent on membrane potential with higher inhibition at more depolarized potentials, suggesting the possibility of relevant effects under such conditions (eg

myocardial ischemia).On hERG- current only a weak inhibition of 7% (n=3) at the highest concentration was determined.

Biological gradient

A clear biological gradient could not be established since blockade of hERG was mild and not seen to increase when doses were increased.

Experimental evidence and ADR reports:

Marilyn et al (2012) found no QT prolonging effects in 32 patients treated with Lacosamide (LCM) 24 hours after LCM initiation, however 3 patients developed prolonged ECG PR intervals. In a randomized trial, healthy volunteers took lacosamide in normal 400 mg/day (maximum-recommended daily dose, 6 days), and supratherapeutic doses and did not prolong the QTc interval. Lacosamide caused a small, dose-related increase in mean PR interval that was not associated with AEs (company report). In a retrospective review of critically ill patients in Status Epilepticus (SE) treated with IV lacosamide by Newey et al (2016) no QT prolongation was observed in the eighty-four patients in SE. Kumar and Jhanjee in their 2010 drug review paper for anti epileptics state that Lacosamide does not have a tendency to prolong the QT/QTc interval or QRS duration and cite several studies to support this. In the 8 post marketing cases assessed, only 3 cases were seen as possibly related to lacosamide but two were not very well documented and the other was in the context of a massive overdose. The remaining 6 cases were seen as uncertain or unlikely to be linked due to late onset of event in 1 case, presence of concomitant drug with known

risk for arrhythmias and QT prolongation in 2 cases, lack of temporality and an inverse dose relationship in 1 case (ADR improved when dose was increased).

Consistency:

No pattern of consistency could be observed.

Specificity:

In preclinical data only a weak inhibition of 7% at the highest concentration was determined. Under the same experimental conditions the reference compound terfenadine at 60 nmol/L elicited a potassium current block of 76%.

Analogy:

There is no apparent analogy in the efficacy or safety parameters of lacosamide when compared to other AED since lacosamide has a distinct and novel mode of action.

Overall assessment:

In the Eudravigilance database the association was disproportionally reported for this drug over others. However literature and case review do not support a relationship with QT prolongation, and preclinical data does not adequately demonstrate a mechanism of action.

3.2.1.6 Levetiracetam: Keppra®

Formulations: Syrup 100mg/mL, 500mg, 1000mg tablets.

Mechanism of action: Is not fully elucidated. Levetiracetam binds to synaptic vesicle protein 2A in the mouse model of epilepsy. The interaction between levetiracetam and the synaptic vesicle protein 2A appears to contribute to the antiepileptic mechanism of action of levetiracetam.

Date EU approval: 29th September 2000

Indication: As monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. As adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy. In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. In the treatment of primary generalised tonic-clonic seizures with Idiopathic Generalised Epilepsy.[12]

Availability in MT: available on GFL

Current SPC wording: QT prolongation is not mentioned in any section

Bradford Hill criteria assessment

Strength of association

1.34 PRR (PRR-0.99/PRR+1.80), 21 ADR reports

[12] Keppra 250, 500, 750 or 1000 mg film-coated tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Nov 16; cited 2017 Feb 02. http://www.ema.europa.eu

Biological plausibility

Preclinical studies did not include effects on hERG. In anaesthetised dogs, levetiracetam, produced transient decrease in blood pressure, tachycardia and atrioventricular block.

Biological gradient

Increased QT interval prolongation was not observed with increasing dose of levetiracetam, however, in cases where QT interval prolongation occurred, reducing the dose, reduced the QT effect in the post marketing cases (positive dechallenge). Direct hERG inhibition data is not available for this product.

Experimental evidence and ADR reports:

In a study on post stroke epileptic patients, a QT prolongation of over 480ms was observed in 4 patients on levetiracetam when compared to the control group. Another patient treated with levetiracetam, remained with a QTc over 500ms. (Siniscalchi et al, 2014). Krishnan and Krishnamurthy report that Levetiracetam, was associated with the longest average QTc (432 ms) intervals in their study on AEDs and antidepressants however in a randomized, controlled study in 52 healthy adult subjects no clinically relevant changes in the QTc interval were observed after a single levetiracetam dose of 1000 or 5000 mg. (Hulhoven et al, 2008)

Of the 19 ADR cases assessed for QT prolongation, the majority had a temporal relationship between the events and the initiation of treatment. 13 cases had confounding

factors, negative dechallenge or presence of electrolyte imbalances and some occurred in the presence of underlying cardiac conditions.

Consistency:

A presentation which included bradycardia and hypotension together with QT prolongation was seen in 3 cases.

Specificity:

Levetiracetam blockade on the hERG potassium channel if any, was not studied.

Analogy:

Levetiracetam has a different mode of action from other anti epileptic drugs. No analogy can be accurately made in this case.

Overall assessment:

In the Eudravigilance database the association of levetiracetam with QT prolongation was disproportionally reported for this drug over others. Literature and case review support a relation between drug and effect. However, overall, the current evidence is not strongly suggestive enough to confirm a safety signal for levetiracetam and ECG QT prolongation with the current knowledge**.**

3.2.1.7 Loxapine: Adesuve®

Formulations: Inhalation powder 4.5mg and 9.1mg for single use, 10mg tablets, 1mg oral solution and I.M injection available.

Mechanism of action: Antagonism of dopamine D2 receptors, 5-HT2A antagonist activity and anti-cholinergic, anti-histaminergic and anti-alpha-adrenergic properties. [13]

Date EU approval: 20th February 2013 (as inhalant), as tablets, oral solution since the 70s.

Indication: For the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder

Availability in MT: not available on government formulary list or private sector.

Current SPC wording:

Section	Wording
4.2 Contraindications	**Not listed**
4.4 Warnings	**Clinically relevant QT prolongation does not appear to be associated with single and repeat doses of Adasuve. Caution should be exercised when Adasuve is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation due to interaction with medicinal products known to prolong QTc interval is unknown.**
4.5 Interactions	**Not listed**
4.8 List of ADRs	**Not listed**
5.0 Pharmacology	**Not listed**

[13] Adesuve EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Oct 15; cited 2016 Dec 29. http://www.ema.europa.eu

Bradford Hill criteria assessment

Strength of association

5.22 PRR (PRR -8.80/ PRR+ 47.89), 10 ADR case reports

Biological plausibility

Loxapine prolonged QT and blocked hERG current *in vitro* at relatively high doses with an IC50 value of (1.8 μM). QTc prolongation was not seen in animal *in vivo* experiments.

Biological gradient

Whether increased blockade of I_{Kr} occurs at increased doses was not investigated in preclinical or postmarketing data available to researcher.

Experimental evidence and ADR reports:

Of the 10 cases assessed, almost all had a temporal relationship between the events and the initiation of treatment however many cases were confounded by other drugs likely to cause QT prolongation or by underlying cardiac conditions. The QT/QTc study did not reveal significant effects after a single dose of loxapine 10 mg on cardiac repolarization as compared to placebo. Simairly QT prolongation was not seen in the repeat dose study by Cassella et al. (2015).

Consistency:

Reports originate from different countries in EU and non EU with possibly different prescribing patters.

Specificity:

In preclinical data loxapine was found to bind the human ether-a-go-go-related gene (hERG) potassium channel, as well as affects AP duration which provides a plausible mechanism for QTc interval prolongation.

Analogy:

Other antipsychotics QTc interval-prolonging/arrhythmic drugs that also bind to hERG provided an analogy for loxapine causing QTc interval prolongation/arrhythmia.

Overall assessment:

In the Eudravigilance database the association was disproportionally reported for Loxapine over others and preclinical data demonstrates a mechanism of action. However literature and case review do not support causality of loxapine induced QT interval prolongation.

3.2.1.8 Mirabegron: Betmiga®

Formulations: 25mg and 50mg prolonged-release tablets

Mechanism of action: Mirabegron relaxes bladder smooth muscle thereby enhancing urine storage function by stimulating beta 3-adrenoceptors in the bladder.

Date EU approval: 20th December 2012

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome [14]

Availability in MT: Not available on the GFL, available in private sector.

Current SPC wording:

Section	Wording
4.3 Contraindications	Not listed
4.4 Warnings	Patients with congenital or acquired QT prolongation. Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed

Bradford Hill criteria assessment

Strength of association

1.22 PRR (PRR-0.64/ PRR+2.35), 15 ADR reports

[14] Betmiga 50 mg prolonged-release tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2015 Oct 15; cited 2016 Dec 29. http://www.ema.europa.eu

Biological plausibility

At much higher doses than those expected clinically, QTc interval prolongation in both dogs and monkeys was seen using the QTc correction method by Bazzett. Mirabegron metabolites M5 and M16 inhibited the hERG channel current with a 50% inhibitory concentration (IC50) of 21 and 31 mcmol/L, respectively at concentrations of 1955- and 2907-fold, higher than the clinical Cmax, at the maximum recommended human dose. Metabolite M14, inhibited 17.3% of the hERG channel current at the highest concentration tested, 30 mcmol/L (2553-fold higher than the clinical Cmax). Inhibitory effects on hERG in pig papillary muscles occurred again only at high concentrations in vitro. These tests show a biological plausibility for a QT prolonging effect in humans, via hERG inhibition, with mirabegrons M5 and M16 and M14 metabolites; however the company states that this would not be expected to occur at clinically relevant concentrations.

Biological gradient

An increase in mirabegron concentration produced an increase in delta QTc in both females and males demonstrating a clear biological gradient for drug concentration and adverse event.

Experimental evidence and ADR reports:

In a study by Malik et al (2012) investigating the proarrhythmic safety of repeat doses of mirabegron in healthy subjects, mirabegron caused QT prolongation at 100 and 200mg

doses (Malik et al, 2012). In a review of the use of Mirabegron in overative bladder syndrome by Sanford (2013) It was stated that mirabegron 50 mg once daily carries a risk (albeit low) of QT interval prolongation (Sanford, 2013). Yamaguchi et al (2015) in a study on safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin found, at end of treatment, that 23.3% experienced treatment emergent adverse evets including 8 patients with QT interval prolongation between 30-60ms. Patients with abnormal electrocardiograms where excluded from this study (Yamaguchi et al, 2015). In another study by Balachandran (2015) which investigated the risk and severity of developing symptomatic palpitations when prescribed mirabegron for overactive bladder 8 patients reported palpitations, two patients with a history of palpitations but no history of prolonged QT interval or arrhythmia on ECG developed worsening palpitations. QTc was prolonged in two patients at 0.458 and 0.441s (QTc <420). Three patients developed chest pain or tightness. The palpitations resolved once therapy was stopped. The authors concluded that palpitations caused by mirabegron may be associated with a worsening of cardiovascular dysfunction (Balachandran and Duckett, 2015). Finally a study by Nozawa et al (2016) it was found that in patients who were given mirabegron and did not have cardiovascular disease, the rate of adverse events was 5.79% while in patients with concomitant cardiovascular disease the total incidence of ADRs was 10.09%. This study showed that patients with concurrent CV disease who take mirabegron are at higher risk of ADRs when compared to other patients. CV ADRs reported during the study period included palpitations (17 events), hypertension (nine events), tachycardia (five events), increased blood pressure (four events), hot flush and cardiac failure (three events each), arrhythmia (two events), supraventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, heart rate increased, deep vein thrombosis, pallor, and N-

terminal prohormone brain natriuretic peptide increased. This study also had a number of drop outs 873/9795 due to none due to ADR (Nozawa et al, 2016). Overall, these studies show evidence for a low but persistent negative effect of mirabegron on the QT interval and cardiac health.

Consistency:

In terms of consistency, 2 post marketing cases had the same profiles, ie. QT prolongation plus ventricular premature contractions and ventricular extrasystoles. Reports originate from different countries, in EU and non EU with possibly different prescribing patters and levels of use. The signal involves both healthy volunteers (experimental evidence) and postmarketing evidence.

Specificity:

In preclinical data mirabegron and its metabolites was found to bind and block the hERG potassium channel and prolong the action potential.

Analogy:

Mirabegron is the only product for OAB authorised in EU which is a selective agonist for human beta 3-adrenoceptor (beta 3-AR).

Overall assessment:

In the Eudravigilance database the association of mirabegron with QT prolongation was disproportionally reported for this drug over others. Literature and case review supports the relation, and preclinical data demonstrates a mechanism of action. The current SmPC for mirabegron does not sufficiently inform on the risk of QT interval prolongation with this drug. Action is warranted to change SPC sections 4.4 and 4.8 on the basis of literature review and case assessment as well as biological plausibility demonstrated by preclinical data. Furthermore, clinicians should be informed of these SPC changes through a direct to healthcare professional communication (DHPC) of the following recommendations;

1. To evaluate patients prior to treatment with mirabegron for risk factors for QT prolongation and if several risk factors are present to use other urologicals with less potential to cause QT prolongation such as the anticholinergic agents oxybutynin and tolterodine.
2. If no alternative can be used, monitoring is recommended. Consider obtaining an ECG and serum potassium levels following initiation of the drug.
3. Additional ECG monitoring should be considered with any dose increase or the addition of other drugs which also carry QT prolongation risk

3.2.1.9 Pantoprazole: Pantoloc Control®

Formulations: 20mg gastro-resistant tablets

Mechanism of action: Pantroprazole inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole is converted to its active form, a cyclic sulphenamide, in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach.

Date EU approval: 12th June 2009

Indication: For short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.[15]

Availability in MT: Available

Current SPC wording: QT prolongation not mentioned anywhere

Bradford Hill criteria assessment

Strength of association

1.00 PRR (PRR-0.69/ PRR+ 1.47), 19 ADR Case reports

Biological plausibility

The preclinical data submitted in this generic dossier was insufficient to characterise any effects on hERG. In the literature 2 indirect mechanisms have been postulated for effect of hypokalaemia (a risk factor for QT interval prolongation)

[15] Pantoloc Control 20 mg gastro-resistant tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2017 Jan 17; cited 2017 Jan 12. Available from http://www.ema.europa.eu

1. via hypomagnaesemia induced kaliuresis (Bibawy et al, 2013) (Hoorn et al, 2010a)

2. via the effect of on the inward rectification of the potassium channels (IKr) by plugging the opened channels as well as modulating the outwardly directed potassium current (Ito). (Bibawy et al, 2013)

Biological gradient

Increased QT interval prolongation was not observed with increasing dose of pantoprazole

Experimental evidence and ADR reports:

Of the 19 cases assessed for QT prolongation, all but 1 had a temporal relationship between the events and the initiation of treatment. Most cases were confounded by other drugs or presence of electrolyte imbalances and some occurred in the presence of underlying cardiac conditions. The majority of cases were assessed as having an Uncertain or Unlikely causality. However 10/19 cases had hypokalaemia occurring within the context of pantoprazole use and in the absence of kidney malfunction or concomitant drugs which cause potassium loss. This pattern of hypokalaemia together with QT prolongation was not observed with any of the other drugs reviewed for association with long QT. Woosley et al (2014) reported that prolonged use of a PPI can cause hypomagnesemia and hypokalemia, conditions that prolong cardiac repolarization and facilitate cardiac arrhythmia and TdP. A biological plausibility has been postulated for chronic PPI therapy and available evidence suggests that this is stronger for pantoprazole than the other PPIs (omeprazole,

esomeprazole, lansoprazole, dexlansoprazole and rabeprazole). In a study by Luk et al (2013); among 66,102 subjects identified as experiencing 1 or more adverse effects while taking a PPI, 1.0% (n = 693) were reported to have hypomagnesemia. The authors conclude that all PPIs were associated with hypomagnesemia, with esomeprazole having the lowest risk and pantoprazole having the highest risk. The risk of PPI-associated hypomagnesemia was higher in males and the elderly population. Hypocalcemia and hypokalemia commonly coexisted with PPI-associated hypomagnesemia (Luk et al, 2013). Negri et al (2013) report a case of a 59 year-old man whose only complaint was gastric irritability with a routine analysis showing hypomagnesaemia and hypokalemia while using esomeprazole, a proton pump inhibitor (PPI). Fractional magnesium excretion was low, excluding excessive renal loss. Potassium excretion was 80 mEq/24 Hr in the presence of hypokalemia suggesting hypomagnesaemia-induced kaliuresis as its cause. Hypomagnesaemia partially resolved after oral magnesium supplementation. Esomeprazol suppression corrected hypomagnesaemia. A causal relationship with esomeprazol use was supported by the recurrence of hypomagnesaemia after rechallenge. A further report by Jhaveri (2012) describes hypomagnesemia in a 65-year-old man presenting with fatigue and muscle weakness. For 3 days he was supplemented with magnesium replacements intravenously and orally with marked improvement, but the cause was unknown. His current morbidities where hypertension and GERD. He had no diarrhea, and no apparent GI loss. He had no history of alcohol ingestion. He was not taking diuretics, and had not been aggressively volume expanded and was not hypercalcemic. The author concludes that it was the PPI which was causing hypomagnesemia. It was also mentioned that hypomagnesemia-induced kaliuresis leading to hypokalemia was seen as well.

Hoorne (2010) attempted to characterize the clinical consequences and possible mechanisms of electrolyte disorders with PPIs using 4 cases. Two men (aged 63 and 81 years) and 2 women (aged 73 and 62 years) had been using a PPI (esomeprazole, pantoprazole, omeprazole, and rabeprazole, 20-40 mg) for 1-13 years. They developed severe hypomagnesemia (magnesium, 0.30 +/- 0.28 mEq/L; reference, 1.40-2.10 mEq/L) with hypocalcemia (calcium, 6.4 +/- 1.8 mg/dL), relative hypoparathyroidism (parathyroid hormone, 43 +/- 6 pg/mL), and extremely low urinary calcium and magnesium excretion. One patient was admitted with postanoxic encephalopathy after a collapse likely caused by arrhythmia. The others had electrocardiogram abnormalities (prolonged QT interval, ST depression, and U waves). Concomitant hypokalemia (potassium, 2.8 +/- 0.1 mEq/L) was considered the trigger for these arrhythmias. Hypomagnesemia-induced kaliuresis (potassium excretion, 65 +/- 24 mEq/L) was identified as the cause of hypokalemia. The authors postulate that this series of PPI-induced hypomagnesemia shows that this is a generic effect and advise that a high index of suspicion is required in PPI users for unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms (Hoorn et al, 2010).

Consistency:

The presence of electrolyte imbalances was seen commonly when assesseing the cases and from literature review. It appears that PPIs cause electrolyte imbalances which have cascading effects.

Specificity:

In preclinical data the block on hERG potassium channel if any was not studied.

Analogy:

The other PPIs do not carry a warning for QT interval prolongation or hypokalaemia.

Overall assessment:

In the Eudravigilance database the association of pantoprazole with QT prolongation was disproportionally reported for this drug over others. However, literature and case review do not support a direct relation between drug and effect, and preclinical data did not demonstrate a direct mechanism of action.

During the course of scientific evaluation of the signal between QT prolongation and pantoprazole an emerging issue became apparent. From the cases assessed, the use of pantoprazole may be the cause of electrolyte disturbances, namely hypomagnesaemia and hypokalaemia. Electrolyte disturbances are major risk factors for QT interval prolongation. While hypomagnesaemia and hyponatraemia are labelled events within the product information of pantoprazole and other proton pump inhibitors (PPIs), hypokalemia is not a labelled effect for pantoprazole or the other PPIs within the EU. In the US, both the FDA and CredibleMeds website (a dedicated website on drug induced QT prolongation) have acknowledged the risk of hypokalemia with pantoprazole. The association between pantoprazole and QT interval prolongation may be an indirect effect of hypermagnaesmia induced kaliuresis ceaused by pantoprazole, or hypokalaemia induced by gastric losses via interference with the H+/K+ ATPase pump as per its primary mode of action. This issue should be assessed separtly in depth.

3.2.1.10 Prucalopride: Resolor®

Formulations: 1mg and 2mg film-coated tablets

Mechanism of action: A novel agent that stimulates gastrointestinal (GI) motility and acts primarily on different parts of the lower GI tract (enterokinetic).

Date EU approval: 15th October 2009

Indication: Treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief. [16]

Availability in MT: Not available

Current SPC wording: QT prolongation not mentioned anywhere.

Bradford Hill criteria assessment

Strength of association

4.50 PRR (PRR-1.46/ PRR+13.89), 3 ADR case reports

Biological plausibility

A modest hERG inhibition in human embryonic kidney cells (HEK293) and action potential duration prolongation in perfused tissues were seen at very high doses highly unlikely to be achieved in man.

[16] Resolor 1 mg film-coated tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2016 Jan 11; cited 2016 Dec 29. Available from http://www.ema.europa.eu

Biological gradient

No increasing QT interval prolongation was seen with increasing doses of prucalopride.

Experimental evidence and ADR reports:

Temporal relationships in the two assessable cases were present but long drawn out and in two cases prucalopride was given with drugs known to prolong the QT interval. Camilleri et al (2009) studied the safety of prucalopride in elderly patients with constipation and found that relative to placebo, there were no differences in vital signs, ECG corrected QT interval, ECG morphology parameters, or incidence of supraventricular or ventricular arrhythmias on Holter monitoring (Camilleri et al, 2009). Frampton (2009) found that in terms of cardiovascular tolerability, the incidence of QT interval prolongation with prucalopride at dosages of 2 and 4 mg/day was low and similar to that with placebo. Moreover, prucalopride at dosages up to 20 mg/day (10-fold higher than the recommended therapeutic dosage) had no clinically relevant effects on cardiovascular parameters in healthy volunteers (Frampton, 2009). Tack et al (2012) in their review of cardiovascular safety of 5-HT(4) agonists developed for gastrointestinal disorders found that cisapride and tegaserod were associated with QT prolongation and ischaemia but not the newer, selective 5-HT(4) agonists such as prucalopride. Finally, in a review of preclinical and clinical data by Shin in 2016 focusing on prucalopride it was concluded that prucalopride has not been associated with adverse cardiovascular side effects or QT prolongation owing to its high selectivity and affinity for the 5-HT4 receptor without clinically significant cross-reactivity at the hERG potassium channel (Shin, 2016).

Consistency:

2 cases were counfounded and do not point to an association, preclinical, clinical and literature data all point against the association of QT prolongation with prucalopride.

Specificity:

Prucalopride has high affinity for and is highly specific to 5-HT4 receptors in the gut.

Analogy:

Prucalopride is the first of a new generation of selective, high-affinity 5-HT4 receptor agonists – no analogy can be drawn.

Overall assessment:

In the Eudravigilance database the association was disproportionally reported for this drug over others, and preclinical data demonstrates a mechanism of action although this occurred at plasma concentrations not achieved with therapeutic doses. Literature and case review do not support the relation.

3.2.2 Short QT investigations

3.2.2.1 Fingolimod: Gilenya®

Formulations: 0.5 mg hard capsules

Mechanism of action: Fingolimod blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, of lymphocytes and reduces nerve inflammation and nervous tissue damage. Animal studies and in vitro experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.

Date EU approval: 21st March 2011

Indication: Gilenya is indicated as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for the following adult patient groups:

- patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or:
- patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. [17]

Availability in MT: Available on government formulary

Current SPC wording: QT shortened not mentioned anywhere.

Bradford Hill criteria assessment

Strength of association

13.69 (PRR-4.33 /PRR+43.26), 4 ADR Case reports

[17] Gilenya 0.5 mg hard capsules EPAR-product information [internet]. London: European Medicines Agency; updated 2017 Mar 10; cited 2016 Dec 12. Available from http://www.ema.europa.eu

Biological plausibility

Fingolimod and its s-enantiomer blocked the hERG channel and Ikr current in in vitro laboratory models (HEK293 cells) by 25.2% and 18.1% respectively. An increased sinus frequency and a slight QT shortening (3%) were observed by both fingolimod and its active metabolite FTY720 P in isolated pig hearts. This therefore provides a plausible mechanism for QTc interval prolongation and arrhythmia but not for QT interval shortening**.**

Biological gradient

Increased blockade of hERG was not seen at increased dose.

Experimental evidence and ADR reports:

Temporal relationships between the events and the initiation of treatment was present in all 4 postmarketing cases, however the QT shortening was insignificant in 1 case, and in the other 3 cases previous cardiac valve disease, minimal information and negative rechallenge did not provide any support for the association.

In the literature Schmouder et al (2006) studied fingolimod effects on cardiac rate and rhythm in healthy subjects but did not specifically investigate the QT interval. The results showed that the first dose of has a mild to moderate negative chronotropic effect (Schmouder et al, 2006) as is listed in the SPC. Yagi et al (2014) investigated QT prolongation effects of fingolimod in a study analyzing the fingolimod-induced atrioventricular conduction block and QT-Interval prolongation. They found that at high

doses, fingolimod prolonged QT interval, and significantly inhibited hERG current. No evidence was mentioned on QT shortening (Yagi et al, 2014). In a study comparing cardiac outcomes in over 3300 patients with relapsing multiple sclerosis in patients taking fingolimod and serotonin-reuptake inhibitors, did not show any QT shortening effects (Bermel et al, 2015). Rossi et al (2015) investigated both QT and PR intervals in an predictive cardiac response study after the first dose of fingolimod and found that while PR intervals increase > 20 ms after fingolimod, no effects were observed on the QT interval (Rossi et al, 2015). Linker et al (2016) observed 217 patients in 42 study centers and concluded that the first-dose observation after fingolimod initiation is usually uneventful even in patients with pre-existing cardiovascular risk factors of this cohort and unlikely to cause QT shortening. They report that rarely observed events remained asymptomatic and self-limited (Linker and Wendt, 2016). Tocci et al (2016) investigated a model using Tp-Te intervals to predict heart rate reduction after fingolimod administration in patients with multiple sclerosis and found that rather short QTc (414.4±24.4 vs. 404.5±24.5ms; $P<0.001$) intervals were recorded but which do not fall under the criteria of short QT (400ms or less) (Tocci et al, 2016). Finally, Turri et al (2017) investigated QTc intervals in patients with multiple sclerosis and there correlation with brain lesions. They found that there was a slightly increased QTc interval in patients with MS and conclude that a cerebral origin possibly driven by involvement of the insular cortex may be the factor responsible for the difference in QT change manifestation in patients.

Consistency:

All post marketing cases originated from the US. The literature was inconsistent with some studies showing prolongation, no effect or slight shortening of the QT with fingolimod.

Specificity:

Fingolimod and its metabolite were found to bind the hERG potassium channel, which provides a plausible mechanism for QTc interval prolongation and arrhythmia but not for QT interval shortening.

Analogy:

No analogy can be drawn in this case.

Overall assessment:

Fingolimod is known to prolong the QT interval but has been reported in a few cases to shorten it as well. This was seen by the statistical disproportionate reporting of QT interval shortening with this drug in the Eudravigilance databas. Upon investigation the cases reported were uncertain and confounded and did not have sufficiently robust information. There is nothing in the literature to support the association and preclinical data does not reveal a hERG attenuating effect. There is insufficient evidence to support the association between Fingolimod and QT shortening.

3.2.2.2 Olanzapine: Zyprexa®

Formulations: 2.5 mg film-coated tablets

Mechanism of action: Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharinmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α1 adrenergic; and histamine H1 receptors.

Date EU approval: 16th November 1997

Indication: Olanzapine is indicated for the treatment of schizophrenia, moderate to severe manic episodes and prevention of recurrence in patients with bipolar disorder).[18]

Availability in MT: Available on government formulary

Current SPC wording: QT shortened not mentioned anywhere.

Bradford Hill criteria assessment

Strength of association

9.09 PRR (PRR-3.69/ PRR+22.38), 4 ADR case reports.

Biological plausibility

There was no preclinical data available in the dossier to assess the effects on hERG since the approval of this product occurred prior to the mandatory requirement to test new active substances for their effects on QT.

[18] Zyprexa 2.5 mg coated tablets EPAR-product information [internet]. London: European Medicines Agency; updated 2017 Mar 21; cited 2017 Feb 12. Available from http://www.ema.europa.eu

Biological gradient

Increased QT interval shortening was not seen with increasing doses of olanzapine from the limited post-marketing studies or cases.

Experimental evidence and ADR reports:

Of the 4 cases assessed, all had a temporal relationship between the events and the initiation of treatment however cases were often confounded by lack of information, lack of dechallenge, or a very small decrease in the QT interval. However, two studies were found to connect olanzapine with short QT. In the Suzuki study (2014) changes in PR and QTc intervals after switching from olanzapine to risperidone in patients with stable schizophrenia were investigated. It was found that all in female patients, the QTc interval was significantly decreased ($t = 3.495,\ P = 0.008$) following the switch, while in male patients, the QTc interval did not change. The initial QT interval in female patients decreased from 410.3 ± 9.5 to 392.1 ± 14.4 and was statistically significant. The study however was small with only 21 patients (Suzuki et al, 2014).

In a larger study by Shafti et al (2014) a comparison between Olanzapine and Risperidone Drug-Induced Electrocardiographic Changes was performed. 268 patients were entered into the open arm study for random assignment. The results showed that while 14.86% and 25% of the cases in the olanzapine group showed prolongation and shortening of QTcF, respectively, comparable changes in the risperidone group were restricted to its prolongation at 32.5% (Shafti and Fallah-Jahromi, 2014).

Consistency:

There is a level of inconsistency in the overall data package with respect to olanzapine especially from the literature search, with numerous publications showing cases of clear QT prolongation and others showing that there could be a QT interval shortening effect. Further inconsistency arises from the fact that QT interval prolongation is a labelled effect of Olanzapine and well documented in the literature.

Specificity:

Data for hERG receptor interaction that may cause QT shortening is not available for olanzapine.

Analogy:

No analogy can be drawn in this case.

Overall assessment:

In the Eudravigilance database the association of olanzapine with QT interval shortening was disproportionally reported for this drug over others. Literature review supports the relation but case review does not support the relation.

3.3 Response from the EMA rapporteurs on signals submitted by Malta

In the EU, a system of rapporteurship exists whereby the safety monitoring of a medicinal product is lead by the country which performed the assessment of the application for a marketing authorisation of an innovator product as lodged by the applicant (the company). For asenapine (Sycrest®) the initial marketing authorisation application was assessed by the UK, making the UK the rapporteurs for subsequent safety evaluations of the product in the later stages of its lifecycle. The same applies for mirabegron (Betmiga®), with Spain having authorised the product thereby making Spain the primary lead responsible for the post marketing safety surveillance (pharmacovigilance) of mirabegron. Nontheless, signals may be picked up by any member state during national reviews and referred to the EMA and the respective rappoerteurs. The responses as extracted from the EPITT software from the UK and Spanish rapporteurs were as follows;

3.3.1 Response from the United Kingdom

EPITT Reference: 18848

"The UK, as rapporteur for asenapine, notes the concern from Malta regarding the issue of the text in 4.4 being potentially contradicatory to the labelling in 4.8 of ECG QT prolonged. This issue of QT prolongation with this product is kept under close review, with the next periodic safety review for asenapine set to start in October 2017. Following the assessment by Malta, it is proposed that the issue of clinical relevance of the QT prolongation is explored in the context of this regulatory procedure. The UK will draft proposals for

clarifying text in the SmPC and support the change if there is evidence this is necessary to avoid misinterpretation."

3.3.2 Response from Spain

EPITT Reference: 18845

"On 27 January 2017, Malta issued a signal on QT prolongation with the use of Mirabegron. Mirabegron is a centrally authorized product indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) being Spain PRAC Rapporteur. The next safety review for this product is expected to start in September 2017. Regarding the Eudravigilance cases, Malta stated that there is a signal of disproportionality, since the PRR is greater than 1 however Spain notes that the confidence interval PRR (-) is 0.64 and not strong enough to warrant immediate investigation. However since QT prolongation is an important potential risk this issue will be closely followed within the next safety review in September 2017. "

Chapter 4: Discussion

In this study, detection of signals and their pharmacovigilance assessment was performed. This was done to assess, using sound clinical judgment, the risks of QT interval change poised by medicinal products. The implications of the findings and observations made are discussed in the coming sections.

4.1 Association between mirabegron and QT interval prolongation

For mirabegron, a previously unidentified risk of QT prolongation was detected and communicated to the European Medicines Agency's rapporteur. The response was that the signal will be further evaluated in the context of an EU wide review in September of this year (2017). While QT prolongation with mirabegron is currently not a listed event in Europe, in the USA and Australia it is listed in the drug's fact sheet[19]. The website CredibleMeds©, lists mirabegron as a drug which prolongs the QT prolongation and possibly induces Torsade de Pointes (Woosley et al, 2017). In correspondence with Dr Ray Woosley, the founder of CredibleMeds and the author of numerous publications on the QT interval, the basis for adding QT prolongation as a known risk was from a dataset which contained 20 cases of QT prolongation from the US's Adverse Event Reporting System (AERS database) as of quarter 3 of 2016. The EB05 for the association, a statistical measure used by the FDA which is similar to the PRR used for this study, was 1.52, which is lower than 2.0, the value at which the signal is considered to be a true signal. Of the 20 cases, 12 had no confounding factors while 8 other cases had other drugs which confounded

[19] Australian Government, Therapeutic Goods Administration. Clinical Evaluation Report for Mirabegron: Proprietry name: Betmiga. Jan 2014.

the picture or the presence of an electrolyte imbalance (hypomagneaseamia). In their dataset there were 3 cases of TdP occurring at doses of 25mg, 50mg and in overdose.

The dataset for mirabegron in the EU used in this study, was smaller. Of the 14 cases available, 8 had no confounding factors. In 6 cases, mirabegron was the only suspect drug and in 4 cases decreases in the dosage or stopping treatment with mirabegron resolved the symptoms (positive dechallenge). Literature review provided additional insight with a small but consistent negative effect of mirabegron on the QT interval and cardiac health observed (Malik et al, 2012; Sanford, 2013; Balachandran and Duckett, 2015; Yamaguchi et al, 2015; Katoh et al, 2016; Nomura et al, 2016; Nozawa et al, 2016). In a pivotal clinical study conducted by the company prior to marketing, a clear biological gradient between the drug and event was demonstrated where it was observed that increased QT interval prolongation was seen with increasing doses of mirabegron, despite the incremental increases falling outside the threshold of regulatory concern. Preclinical studies showed a biological plausibility for a QT prolongation effect in humans, via hERG inhibition from mirabegrons' M5, M16 and M14 metabolites. Since these occurred at doses well above the expected Cmax in humans, at the time it was not expected to occur in patients when mirabegron is used as intended.

Mirabegron appears not to pose a substantial cardiovascular risk in the younger healthier patient. It is when mirabegron is taken in overdose or in patients with concurrent cardiovascular (CV) disease, that the risk of arrhythmias is increased as seen in the study by Nozawa et al (2016) where patients in the mirabegron arm with previously existing CV

disease experienced excess incidence rates of ADRs of 4.3% when compared to mirabegron treated patients who did not have concurrent CV disease (10.09% vs 5.79%) (Nozawa et al, 2016).

Enough evidence to warrant the inclusion of this adverse event into the products label has been put forward in this study. In order to avoid the use of this drug in combination with other QT prolonging drugs the adverse event needs to be labeled and healthcare providers advised of the new label.

4.2 Asenapine and QT prolongation

The case of asenapine highlighted an important issue within the EU system regarding data quality within the SPC and the potential to include contradictory statements within it.

In the asenapine clinical development program, QT prolongation was observed in sufficient rates to be included within section 4.8 as a listed event with frequency uncommon. Section 4.4 on warnings and precautions goes on to state that 'Clinically relevant QT prolongation is not expected with asenapine' thereby allowing for misinterpretation, and a false sense of reassurance to prescribe this drug in patients who are predisposed to QT prolongation. Knowing the risk a drug carries for QT prolongation may prompt, at the very least, a baseline ECG, a follow up in patients who are at risk, or the withdrawal of the drug once QT prolongation is experienced.

In Europe, asenapine is indicated in the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults while in the USA, it is also approved for the

treatment of schizophrenia. It is known that severe mental illness is associated with poorer health outcomes (Phelan et al, 2001) and persons with schizophrenia, are reported to die an average of 10 to 15 years earlier than the general population, mostly as a result of cardiovascular risk (Newman and Bland, 1991; Brown, 1997). In a study by Linzer in psychiatric outpatients, in which routine ECG testing was performed, over 50% had concerning findings, with older patients with multiple comorbidities being at higher risk of having an abnormal ECG (Linzer et al, 2013). The authors contend that iatrogenic effects were the main cause for the abnormalities. It is to be kept in mind that psychiatric patients often lead unhealthy lifestyles, which adds to the risk for CV disease. Antipsychotic medications can also cause metabolic disorders affecting cholesterol levels and causing type II diabetes, important risk factors for CV disease. Greater importance toward minimizing CV risks should be taken in these patients as they are more likely to have multiple risk factors. Interestingly, in some countries, the interpretation of ECGs in psychiatric patients has become routine practice (Heiselman et al, 2012).

This study identified a number of medications associated with QT modulation which treat psychiatric disorders. From the 12 in-depth assessments performed, one third were on antipsychotic or antidepressant medications (agomelatine, asenapine, loxapine and olanzapine) with a further 2 (lacosamide and levtiracetam) used in the treatment of epilepsy. This parallels previous findings that these classes of medication are often associated with QT prolongation and place patients at added risk of arrhythmias and sudden death. Vigilance in prescribing and monitoring of these drugs is essential in these patients.

4.3 Findings on QT shortening

The arrhythmogenic potential of short QT intervals has been highlighted in patients with the genetic form of Short QT syndrome, however, as seen from this study, reports on drug-induced short QT are rare and confusing since some of the drugs reported to cause QT shortening are also able to prolong the QT. The current theory for QT shortening is a gain in function of potassium channels, enabling a rapid greater influx of potassium ions. However, in the case of rufinamide, the only drug which contains a labeled warning against short QT, this is not the case and it was found to have no effect on hERG current when investigated in human embryonic kidney cells (Shah, 2010). The reason for the QT-interval shortening effect with rufinamide still remains to be elucidated (Shah, 2010).

This study identified 13 signals of short QT within 195 ADR reports on drugs with short QT, specifically, on carbamazepine, clozapine, digoxin, fingolimod, ibuprofen, olanzapine, paracetamol, quetiapine, ramipril, simvastatin, ziprasidone, atenolol and calcium carbonate. Of these drugs, digoxin is known to cause short QT and increased cellular repolarisation and shortens the duration of the action potential (Cheng, 2004).

This cannot be said for the other drugs identified, as these are drugs known to prolong QT (carbamazepine, clozapine, fingolimod, olanzapine, quetiapine, ziprasidone, atenolol) with numerous reports, studies, labels and literature cases highlighting the association between these drugs and QT prolongation. In the case of dexmedetomide which is not known to cause either QT prolongation or QT shortening according to the SPC, it was seen from the literature that both prolongation and shortening were experienced in clinical trials. Dexmedetomidine is an agent used for rapid anaesthesia in the Intensive Care Unit setting and was reported in three independent studies to shorten the QT. Literature cases of QT

prolongation with dexmedetomidine were then also reported as well as postmarketing ADR case reports (see Results section 3.2.1.3). From this study, the evidence on QT prolongation with dexmedetomidine was not strong enough for a recommendation to change the SPC, however in the US dexmedetomidine has been added to the list of medications with possible risk of prolonging the QT interval and/or inducing TdP on the CredibleMeds® site.

In the case of Fingolimod and Olanzapine, despite the information available being too sparse to recommend changes the same dual effect occurred. In the literature, conflicting reports are available also on carbamazepine, phenytoin and primidone, with some indicating that they shorten QTc (DeSilvey and Moss, 1980; Kenneback et al, 1991; Wyte and Berk, 1991).

Overall, this study findings suggest that there may be an alternate pharmacological mechanism which may be independent of hERG is occurring when there are QT shortening effects, which is not yet fully understood.

4.4 Pantoprazole and signal of hypokalemia

Pantoprazole was among the 10 drugs assessed for QT prolongation. Of the 19 unique cases reported for QT prolongation with pantoprazole the majority were assessed as having an Uncertain or Unlikely causality. This happened because most cases were confounded by the presence of an electrolyte imbalance, by cardiac conditions or by other drugs known to prolong QT. Strikingly, 10/19 cases had hypokalaemia reported within the context of pantoprazole use, and in the absence of kidney malfunction or concomitant drugs which cause potassium loss. In the other 9 cases, the presence of hypokalaemia could not be

excluded. This pattern of hypokalaemia together with QT prolongation was not observed with any of the other drugs reviewed for association with long QT.

Hypokalemia is not a labeled effect for pantoprazole in the EU although several articles in the literature have documented hypokalaemia or hypomagnesaemia, which can, in turn induce hypokalaemia (Flockhart et al, 2000; Perri et al, 2001). Jhaveri and Woosley et al, have reported that prolonged use of a PPI can cause hypomagnesemia and hypokalemia, conditions that prolong cardiac repolarization and facilitate torsades de pointes (TdP) cardiac arrhythmia (Jhaveri, 2012; Woosley et al, 2017). Available evidence supports a stronger effect for pantoprazole than the other PPIs (omeprazole, esomeprazole, lansoprazole, dexlansoprazole and rabeprazole) (Hoorn et al, 2010; Luk et al, 2013). For CredibleMeds©, pantoprazole was classified as carrying a risk for TdP since it can cause hypomagnesemia and/or hypokalemia and indirectly result in arrhythmia. In a study by Luk et al in over 66,000 subjects, 1.0% (n = 693) were reported to have hypomagnesemia (Luk et al, 2013), with a higher prevalence in males and elderly. A strong association between hypomagnesemia and both hypocalcemia and hypokalemia was demonstrated (Luk et al, 2013). Literature cases by Hoorn et al (2010b); Negri and Valle (2011) and Jhaveri (2012) also support this association.

The issue of hypokalemia induced by PPIs is an important emergent signal that could warrant full in depth investigation. In terms of QT prolongation with pantoprazole, there is a level of unease with excluding the signal however as per study protocol the results obtained were through application of standard causality assessment method and their scoring systems. A possible QT prolongation effect which is masked through hypokalaemia is not excluded in

this case. Alternative methods of case assessment should be considered for future signal detection on this product.

4.5 Reflections on including preclinical data in signal detection

The use of preclinical data in signal detection is not routine practice in the EU[20]. In this study, preclinical data was used to establish whether a biologically plausible mechanism exists for the ADR to occur. Out of the ten signals reviewed, 7 products had a hERG blocking effect at unphysiological concentrations in preclinical data. Case evaluations of post marketing setting then showed QT effects occurring even at therapeutic doses, especially when other contributing factors create the perfect conditions for TdP. These results show that it is wise for assessors who observe even low hERG channel blockade in animal studies, to factor this information within the risk management strategy for the drug as a potential risk. Preclinical studies should not be considered in isolation as an absolute criterion for deciding whether or not to continue further development, however these studies are important in identifying areas which require future monitoring and any hits at that stage should be thoroughly investigated at the licensing stage by the company and assessors.

[20] Pharmacovigilance Risk Assessment Committee; Recommendations on safety signals, monthly overviews. Accessed June 2017
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp

4.6 Regulatory implications

The regulatory management of medicinal products affecting the QT interval is only one aspect within an overall strategy aimed at improving the benefit risk balance of authorised products. In the final prescriber-patient step, whether or not a patient will benefit from detailed prescribing information depends on the patient and his/her prescribing physician (Schachtele et al, 2016). The level of physician compliance with prescribing restrictions and monitoring requirements to date is not encouraging. In a number of surveys relating to terfenadine (Lu et al, 2001; Puglisi and Bers, 2001) and cisapride (Webster et al, 2002), there was significant, inappropriate prescription of these drugs to patients at increased risk. A study was done to check the adherence to recommendations within a direct to healthcare professional communication (DHPC) issued by the national regulatory agency regarding contraindicated co-prescriptions with the QT-interval prolonging antidepressants citalopram and escitalopram (Schachtele et al, 2014). It was observed that prescriptions of contraindicated combinations of citalopram and escitalopram with other QT-drugs did not decrease significantly after the release of corresponding warnings by the German Drug Authority (Schachtele et al, 2014). Schatele and colleagues acknowledge that this is in part attributable to the fact that the physicians are left the laborious task of identifying all QT-relevant drugs and drug–drug combinations in their polymedicated patients (Schachtele et al, 2016). Monitoring requirements such as baseline and/or periodic ECGs also are ignored in many cases (Schachtele et al, 2016).

Regulatory authorities are aware of the above issues and to what extent there is likely compliance with complex prescribing information and monitoring requirements (Schachtele et al, 2016). In contrast, much greater scrutiny and importance is attached to the product

information when this is under evaluation in court. In the US, the *Mulder* rule, states that: "Where a manufacturer recommends to the medical profession 1) the conditions under which its drug should be prescribed; 2) the disorders it is designed to relieve; 3) the precautionary measures which should be observed; and 4) warns of the dangers which are inherent in its use, a doctor's deviation from such recommendations is prima facie evidence of negligence if there is competent medical testimony that his patient's injury or death resulted from the doctor's failure to adhere to the recommendations" (Thornton, 2003). This rule was subsequently modified to state that for a package insert to be considered evidence of the standard of care, the package insert's recommendations and instructions must be "clear and unambiguous" (Thornton, 2003).

The current state of play in Europe is that there are no official and validated reference lists for drug affecting the QT interval or particularly dangerous drug-drug combinations. This makes it difficult for the physicians to recognize the problematic drugs at prescribing stage. This study attempted to initiate such a list of QT risk and grade the risk of QT through the frequency categorisation approach as was done in Table 2.

The US list CredibleMeds focuses on the QT-and arrhythmia risk of individual drugs, however the co prescription of combinations of two or more QT-drugs which cannot be avoided carries a new additive risk which as yet has not been addressed. This study has proposed a risk stratification based on frequency, ex risk of 1/10 (very common frequency) vs rare frequency (≥1/10,000 to 1/1000). This could aid in the selection of drugs within the same theraupetic class based on expected risk. Further studies to test the pragmatic usefulness of such a strategy would be needed before any conclusions can be made.

4.7 Study recommendations

1. Signal detection using a triage of preclinical, clinical and literature data as used in this study is a way to identify signals early on after a product is placed on the market. In routine practice, the preclinical component is rarely included for signal detection as can be seen in the publically available PRAC signal recommendations monthly overviews and the data sources used therein (PRAC, 2017). It is recommended that the preclinical component in data assessment is incorporated into safety signals in order to establish biological and pharmacological plausibility of drug effects.

2. Assessors and marketing authorization holders are advised that when looking at preclinical data, they should not be reassured by hERG blockade reported to occur only at unphysiologically high doses. When such an observation is made, the risk should be flagged as a potential risk within the risk management plan of the medicinal product for close monitoring in the post-licensing phase.

3. It was observed that QT shortening may occur with drugs that prolong the QT and that mechanisms of QT shortening cannot be explained solely by activation of potassium channels. Further research into other electrophysiological causes affecting the gating of hERG should be pursued.

4. A list of QT prolonging drugs was developed with a risk stratification proposal based on frequency of occurrence. This needs to be further developed since it currently only contains CAPs. It is recommended that a risk sheet for all drugs found to modulate the QT interval is published and updated regularly and made available to prescribers, pharmacists and patients. This strategy could increase vigilance in mornitoring of any therapy related cardiac events when patients are on concomitant multiple QT prolonging drugs including over the counter products.

4.8 Study limitations

4.8.1 Underreporting

The main disadvantage of spontaneous reporting is the potential for underreporting. Visacri *et al.* in 2015 reports that only 6% of all occurring ADRs are reported. Aurora (2012) has shown that for every adverse event captured by spontaneous reporting, 10 others remain unreported. Spontaneous reporting to adverse event database is at times not enough to clearly capture the post marketing experience of a medicinal product. Underreporting of ADRs may lead to the false sense of security that a real risk is absent when it is actually present.

4.8.2 Coding of ADRs

Medical coding is the process of transforming descriptions of ADRs into universal medical terms with the help of drug dictionaries such as MedDRA and WHO-ART (Aurora, 2012; Kumar and Khan, 2015). Within the Eudravigilance database, the MedDRA dictionary is

used. MedDRA is a clinically validated international medical terminology used by the regulatory authorities and the regulated bio pharmaceutical industries throughout the entire regulatory process, from pre- marketing to post-marketing activities & for data entry, retrieval, evaluation & presentation. A limitation is that different countries populating the database may have different coding practices. Interstitial coronary artery disease for example, may be coded as atherosclerosis or induration of the arteries in another. Therefore cases which may have been coded under different terms from QT prolongation/shortening, or mentioned QT prolongation only in the case narrative and had other adverse events such as sudden death entered into the adverse event data field could have been missed. However, these cases are expected to be low since this type of inputting by the regulatory authorities or marketing authorization holders is erroneous and not in line with coding principles outlined in MedDRA guidelines and mandatory training programs for operators of the Eudravigilance database.

4.8.3 QT interval measurements

Another limitation was that retrospective QT interval measurements were used as reported in the ADR reports. There was no possibility to verify the accuracy of QT interval measurements using a consistent method of assessment.

4.9 Conclusions

The QT change potential of drugs was found to be well-reflected in the product information of 51 centrally authorized products and potentially requiring change for 12 products. After full assessment, (a) a safety signal for mirabegron and QT prolongation was identified and presented to Spain as rapporteurs, (b) a conflicting statement in the SPC of asenapine was identified and evidence to support the removal of the statement was presented to UK rapporteurs and (c) a potential signal of hypokaleamia with pantoprazole was identified which could warrant further investigation. In relation to short QT, it was observed that QT shortening may occur with drugs that prolong the QT and that the mechanisms of QT shortening cannot be explained solely by activation of potassium channels. Assessors and marketing authorization holders are advised that when looking at preclinical data, they should not be reassured by hERG blockade reported to occur only at unphysiologically high doses. When such an observation is made, the risk should be flagged as a potential risk within the risk management plan of the medicinal product for close monitoring in the post-licensing phase. Finally, the pilot list of QT prolonging drugs developed for this study contains a risk stratification proposal based on frequency of occurrence which if expanded can offer an advantage over existing QT drugs lists for EU healthcare providers and citizens.

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Appendix 1:

Background to the Method

Study 1: Using ADR reports in Eudravigilance for signals of disproportionate reporting

Eudravigilance is a database of ADR reports for drugs and biologics that is hosted by the European Medicines Agency (EMA) as a post-marketing safety-monitoring tool. This database is populated by regulatory authorities and by marketing authorisation holders across Europe and contains around 5 million reports (European Medicines Agency, 2016). Data are made available through the European Commission's page www.adrreports.eu for the general public and through the Eudravigilance Data Analysis Software (EVDAS) for the regulatory authorities. EVDAS is a data mining tool developed to support the EMA and EU member states in their signal detection activities. The Eudravigilance dataset can be queried in various ways to retrieve ADR reports related to a set of parameters; for example, all ADR reports related to QT prolongation, with fingolimod as suspect drug, over a set time period. For this study, the database was queried to retrieve reports of QT prolongation[1] from 1st January 2004 to 31st August 2016. The question asked to the database essentially was to find which medicinal products have been reported to cause QT prolongation AND have a Proportional Reporting Ratio of 1 or more, AND have at least 3 reported cases.

The Proportional Reporting Ratio

The Proportional Reporting Ratio (PRR) denotes whether the number of cases reported in the Eudravigilance database (observed cases) exceeds what might be expected due to chance. To check for observed rates versus expected rates there are several accepted approaches (CIOMS, 2010). The first of these approaches involves using denominator data related to use of the drug (in the form of dispensed prescriptions or sales figures) and calculating reporting rates, (number of ADR reports/ number of prescriptions) (Evans et al, 2001). With this method biases may arise by factors such as increased reporting for new drugs and the effects of publicity (Evans et al, 2001). Miniumum importance can be placed on small differences in reporting rates between drugs but large differences (many fold) may represent a signal worthy of investigation (Evans et al, 2001).

The second approach and the one used for this study is to use the total number of reports for the drug as a denominator and to calculate the proportion of all reactions from ones of interest (such as reports on QT prolongation with fingolimod vs all other reports on a fingolimod). This calculation method which uses the stability of a large database to calculate the proportion of specified reactions or groups of reactions of interest where the comparator is all other drugs in the database is the proportional reporting ratio (PRR).

In a two by two table, the PRR is A/(A+C) divided by B(B+D) (See Table 1 adopted from Lemery et al) (Lemery, 2011)

[1] The same was done to retrieve denominator data for QT shortening. The same method was applied for detecting signals of QT shortening and so the two terms are used interchangeably in the method section.

Table 1: Signal detection two by two table

	Event of interest	**All other events**	**Total**
Product of interest	A	B	A+B
All other products	C	D	C+D
Total	A+C	B+D	A+B+C+D

A is the event of interest for the product of interest. B is all other events with the product of interest. C is the event of interest in all other products. D is all other events in all other products.

An example of such a calculation is given in Table 2 below adopted from Evans et al, 2001.

Table 2: Example of a PRR calculation-rifabutin and uveitis

	Rifabutin	All other drugs
Uveitis	41	754
All other ADRs	14	591 958
TOTAL	55	592 712

PRR = 41/55 divided by 754/592, 712 = 586.
Chi-squared (1 df) = 22 740.

This PRR may be compared with the value for other drugs. This proportionate approach has advantages over the reporting rates method. No external data is needed and problems of access and delay in receipt of data do not apply. Also, the PRR method may be expected to counteract some of the biases related to variable reporting. If the overall level of reporting is high because of new drug bias, (typically there is a higher reporting rate in the early years of a product's life followed by a subsequent decline (Moulis et al, 2012) this will not necessarily affect the proportion of all reactions for the drug which are of a specified type (Evans et al, 2001).

The expected value for a PRR is one (similar to the epidemiological concept of a relative risk of one) and the values generated are measures related to strength of association; the higher the PRR, the greater the strength of the signal. If a PRR is less than 1 it means that there are less reports than expected for that drug and event pair (Gogolak, 2003).

It is also possible to measure the size of the association using an odds ratio and values for Chi Square (Evans et al, 2001). The decision about whether or not there is a signal, and its strength, is made by evaluating three pieces of information ie. the PRR, value of chi-squared and the absolute number of reports (Grundmark et al, 2014).

Grundmark and colleagues in their review and comparison of the PRR method to other methods determined a high level of sensitivity for the PRR (Grundmark et al, 2014) and so this method was chosen for this study.

Bradford Hill criteria as applied to pharmacovigilance

Permission to use the criteria was obtained from SAGE publications as per below;

From: PermissionsUK [mailto:PermissionsUK@sagepub.com]
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Sir Austin Bradford Hill in his paper on environmental association to disease and public health, proposed nine criteria to be used in assessing cause and effect (Hill, 1965). These criteria for attributing disease causation to environmental factors have been used widely in epidemiology but are also applicable to pharmacovigilance and pharmacoepidemiology (Shakir and Layton, 2002;Perrio et al, 2007).

The 9 criteria are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. The following is a brief explanation of the nine Bradford Hill criteria.. The Bradford-Hill criteria assessment framework given in Table 3 provides a description of how each criterion was applied for this study.

1. Strength

Strong associations are more likely to be causal than weak associations which are more likely to be explained by unrelated biases. In pharmacovigilance, the proportional reporting rates (PRR) indicates that if an event has been reported more frequently with a product, this may indicate a safety signal. The higher the PRR, the stronger the evidence for the signal.

2. Consistency

For consistency of findings, if the same observation occurred in different populations under different circumstances then this provides additional support for a causal association. It is important to use as many data sources as possible to assess a causal relationship between drug and event. In the Eudravigilance database there will be reports originating from both hospital and community settings in different countries. Having the same event reported consistently from different settings further highlights an association.

3. Specificity of the Association

Hill stated that a cause leads to a single effect not multiple effects, but cautioned that this concept of specificity is not always applicable. In drug safety monitoring, drugs cause ADRs by specific mechanisms which may or may not be known at any one time. True associations are specific, and in many circumstances it is not plausible that a drug is associated with an increase in developing multiple cancers for example.

4. Temporality

It is necessary that a cause precedes the effect in time. ADRs occur in patterns based on a relation to exposure, the pharmacological characteristics of the drug and a person's response to the drug. A consistent pattern with regard to temporal relationship is important in assessing a causal relationship.

5. Biological Gradient

The biological gradient or dose response curve is well known in epidemiology (Shakir and Layton, 2002). For example, the number of cigarettes smoked and the number of years of smoking are directly related to the development of carcinoma and cardiovascular disease (Shakir and Layton, 2002). Care must be taken when assessing biological gradients as these can sometimes be misleading. For example, excessive drinking of alcohol is associated with detrimental dose-related effects, while drinking small amounts of alcohol can be protective (Burns et al, 2001). In this study a causal association will be supported when an ADR occurs in a dose-dependent manner or from cumulative exposure over a prolonged period of time.

6. Plausibility

Biological plausibility in drug safety monitoring refers to the mechanism by which a drug is causing the adverse event. In some cases this is known, for example, if a new nonsteroidal anti-inflammatory drug is marketed which causes gastrointestinal bleeding then we know that the adverse event is biologically plausible via COX-2 enzyme inhibition (Hardman and Limbird, 2001). However, in novel associations this may not be straight forward and might require substantial research into the modes of action of the drugs to infer a possible plausibility.

7. Coherence

Hill defined coherence as the cause-and-effect interpretation whose data should not seriously conflict with generally known facts of the natural history and biology of a disease (Hill, 1965).

8. Experimental Evidence

Experimental evidence as a supporter for causal inference is self-evident. Studies in biological models as well as animal and human experiments all lend support to signals raised in pharmacovigilance. It is often necessary to conduct studies to better understand signals generated. This can be mandated from marketing authorisation holders in the form of PAES or PASS (Post Authorisation Efficacy or Safety Studies) by the European Medicines Agency or national competent authorities as an output of Council Directive 2010/84/EU.

9. Analogy

In drug safety, analogies are frequently used to support assertions that the safety profile of a particular product is similar to others in the same therapeutic class. For example, in evaluating ADR reports of cough with losartan an angiotensin II antagonist, an analogy with the other angiotensin II antagonists can be proposed based on the pharmacological actions of the group.

Table 3: The Bradford-Hill criteria as used for this study and data sources.

Criterium	Source
Strength of association and coherence Are there more reports of associations between the suspect drug and QT prolongation or TdP than would be expected by chance alone? Are there associations with palpitations, syncope sudden death or other events know to be associated with long/short QT	Eudravigilance database
Biologically Plausible Mechanism Does the suspect drug prolong QT or block the hERG channel or Ikr current in *in vitro* laboratory models?	Preclinical data in CTD module 4,Literature
Biological Gradient Is there evidence of dose/concentration response in clinical and/laboratory data?	Preclinical data in CTD module 4, Literature
Experimental evidence and Temporality Do clinical studies demonstrate that exposure to the suspect drug is followed by QT prolongation and/or TdP? Is there evidence of reversal with de-challenge?	ADR reports, Clinical trial data in CTD module 5, Literature
Consistency Do clinical studies show consistent results for QT prolongation and/or TdP	ADR reports, Clinical trial data in CTD module 5, Literature
Specificity Do clinical cases or studies report the usual associations with TdP (hypokalemia, bradycardia, drug-drug interactions) and lack evidence for alternative explanations (history of seizures, myocardial infarction)?	ADR reports, Clinical trial data in CTD module 5, Literature
Analogy Do chemically similar drugs have the ability to prolong QT and cause TdP?	SmPCs across drug classes

Data utilisation

The second study consisted of linking the data obtained from the signal detection and expectedness check in order to perform a full evaluation of previously unknown signals of QT prolongation or shortening. The full evaluation was done keeping the above BH principles in mind.

ADR reports

ADRs are reported based on a suspicion of a healthcare professional or a patient that a drug caused an adverse event. When a single drug is given in a relatively healthy patient and this patient experiences an ADR close to the time of administration then assigning causality is easy and will most be seen as highly probably related to the drug. Many times it is not always that easy and therefore specific algorithms to standardise the method of causality assessments have been devised. This is helpful since without such methods, there would be too much subjectivity within the process.

A large bulk of the work for this study was assessing the ADRs reported to assign a causality score. Summaries of the ADR reports and their causality assessments are appended within a specific products file. When one downloads data from Eudravigilance, it comes in the form of a HTML which is largely unstructured data and so substantial efforts in cleaning the data and summarising had to be deployed.

Causality assessment

Currently there is no universally accepted method for assessing causality of ADRs, however the most widely used is the French tool (Andrews & Mann, 2002). Other methods described in the literature are: the 9 points of consideration – Morges, Switzerland, 1981), Probability calculation (Bayes' Theorem). Aetiological – Diagnostic Systems (Bénchiou's group method), the European ABO Systems, the US Reasonable Possibility Systems, the Naranjo''s ADR Probability Scale, WHO Causality Categories, Jones' algorithm, Yale algorithm, Karch and Lasagna algorithm, Begaud algorithm, Newer quantitative approach algorithm, Venulet' algorithm, Emanuelli' algorithm, Gallagher' algorithm and Kramer' algorithm. In keeping with the method of choice of the local national competent authority, the Malta Medicines Authority, the French tool of causality assessment was used.

French tool

The basic principles of the French method for assessing causality are described in Andrews & Mann and entail-

- That the causality be judged only on the data present in the case, in abstraction of all published data concerning the drug-reaction association. Each case is judged on its own merits to ensure maximal identification of possible new reactions.

- That the causality be assessed on each drug-reaction pair presented by the patient at the time of the event, or that could be involved (such as previously stopped medication that could result in unidentified withdrawal symptoms).

The system uses 6 main criteria, three for chronology (time-sequence), and three for semiology (signs and symptoms). The time sequency analysis criteria include challenge, dechallenge and rechallenge. The signs and symptoms criteria are pharmacological plausability, other causes for event and laboratory test results. The outputs feed into a three way table.

The scores are:

– *Highly probable***:** a clinical event occurring in a plausible time relative to drug administration and which cannot be explained by concurrent disease. The response to withdrawal of the drug (dechallenge) should be clinically plausible, with a satisfactory rechallenge procedure if necessary.

– *Probable:* is a clinical event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease, and which follows a clinically reasonable response on withdrawal (dechallenge).

– *Possible*: a clinical event, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease. Information on drug withdrawal may be lacking or unclear.

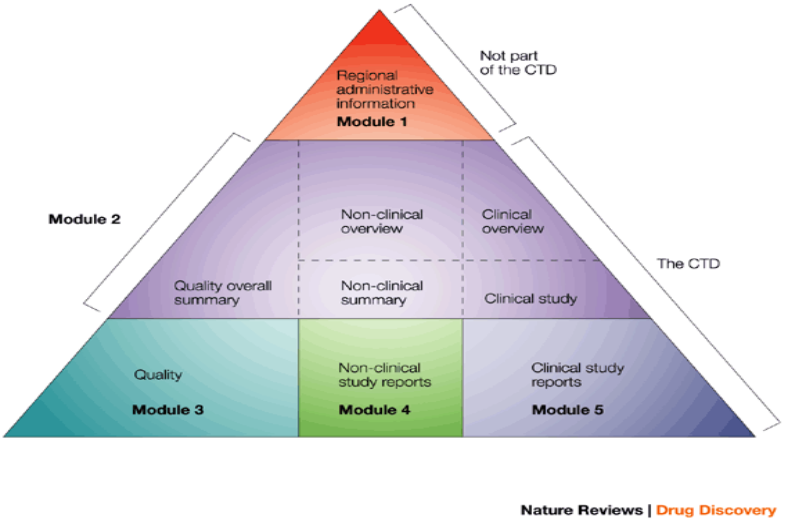
-*Uncertain*: a clinical event with a temporal relationship to the drugs administration in which other explanations and confounding factors make attribution to the drug doubtful however the association cannot be excluded.

–*Unlikely*: clinical event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which underlying disease or other drugs provide more plausible explanations.

Dossier data

The drug dossier is a collection of documents grouped together to describe all the technical aspects of a medicinal product as shown in Figure 8. It is this document which forms the basis for a marketing authorisation. The dossier is organised into five modules. Module 1 is specific to the it is being submitted to and Modules 2, 3, 4 and 5 are intended to be common for all regions.

Figure 9: A medicinal products full dossier, showing module 1 and modules 2-5. (Molzon J, 2003.)



Appendix 2:
Asenapine

Malta, 03 January2017

Signal Description Message

From	To	Copy to
Amy Tanti	Post-Licensing Directorate	Professor John J Borg

Subject

Medicinal product	Asenapine (Syncrest® 5 mg and 10 mg sublingual tablets)
Signal (MedDRA term)	Electrocardiogram QT interval prolonged

Priority Grade Proposal:

Important risk

Summary

Imputability Score	Number of case
I0 -Unlikely	0
I4-Highly Probable	0
I2-Possible	1
I3-Probable	5
I1-Uncertain	11

Signal characteristics

Source (database, literature…)	Eudravigilance database, medical literature, company clinical and pre-clinical data
Number of reports	25 (8 duplicates) 17 cases, 16 assessable 3 EU and 14 non-EU (13 assessable) Literature review:
Expectedness	Yes in section 4.8 but conflicting evidence in 4.4
Seriousness	Yes Drug induced QT interval prolongation predisposes to arrhythmias, including the lethal Torsade de Pointes.
Statistics (if available, e.g. PRR, IC, confidence interval…)	Reaction PT | PRR (-) | PRR | PRR (+) | Static PRR Analysis - CHI^2

	Electrocardiogram QT prolonged	3.2892979	4.8584388	7.17612932	76.6262426
Estimate of exposure	48,840 patient-years of treatment with asenapine in the past year (Aug 2015 – Aug 2016)				

Asenapine: Syncrest® 5 mg and 10 mg sublingual tablets

Mechanism of action: not fully understood however based on receptor pharmacology, proposed that efficacy is mediated mainly through antagonist activity at D2 and 5-HT2A receptors.

Date EU approval: 01 September 2010

Indication: treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

Availability in MT: not available on government formulary list

Currently authorised SmPC wording:

Section	**Wording**
4.2 Contraindications	Not listed
4.4 Warnings	*Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.*
4.5 Interactions	Not listed
4.8 List of ADRs	*Listed; frequency uncommon*
5.0 Pharmacology	Not listed

Summary of company preclinical data

Cardiovascular studies in anesthetized cats, anesthetized dogs and conscious rabbits indicate that the main hemodynamic effects of intravenous asenapine are a decrease in arterial blood pressure and orthostatic hypotension. In conscious dogs, orally administered asenapine induced dose-dependent negative inotropic and positive chronotropic effects accompanied by ECG changes (QTc interval prolongation), orthostatic hypotension on tilt with marked tachycardia. Sublingually administered asenapine had fewer side-effects even at doses yielding similar asenapine plasma levels. The effects after sublingual administration were dose-dependent tachycardia in the absence of negative inotropy and hypotension. Furthermore, after passive tilt, modest orthostatic hypotension was observed accompanied by an augmented orthostatic rise in heart rate. The company states that both effects can be attributed to asenapine's alpha-adrenergic antagonistic activity, although asenapine's strong influence on serotonergic receptors may also play a role in the observed effects.

Studies in isolated rabbit and guinea-pig cardiac muscle and rabbit aortic tissue suggest that the cardiovascular effects observed in vivo are not related to effects on voltage operated ion channels. Studies to evaluate effects on cardiac repolarisation showed that when tested in the hERG assay the extrapolated IC20 for asenapine (42 nmol•L-1 = 12 ng•mL-1) was 67-fold greater than its estimated efficacious free concentration in human (0.18 ng•mL-1 at 10 mg b.i.d.). Similarly, its N-desmethyl metabolite, is not expected to interact with the hERG channel at clinically relevant concentrations (extrapolated IC20 = 0.2 μmol•L-1). The N+-glucuronide metabolite had no hERG activity. The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD50. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33 Hz) than under normal stimulation rates(1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD50) but at approximately 10 times higher concentrations. QTc interval data from the above mentioned cardiovascular safety study in conscious dogs were evaluated. As heart rate was increased in these dogs after oral and sublingual administration of asenapine, analysis of the data was conducted using Fridericia's (QTcF) and van de Water's correction (QTcVdW) rather than Bazett's correction (QTcB). QTcF and QTcVdW prolongation was minimal (approximately 15 msec higher than controls at low dose) after oral administration and the increases did not appear to be dose-dependent. After sublingual administration, no statistically significant prolongation of the QTcF and QTcVdW intervals relative to controls was observed.

Reviewer conclusions: *Asenapine and its metabolites modify arterial blood pressure and heart rate. Asenapine shortens the action potential duration and blocks the hERG channel in vitro at high doses. Sublingually administered asenapine (as is currently authorised for use in EU) had fewer cardiovascular effects however QTc prolongation was observed for both sublingual (not statistically significant) and oral formulations.*

Summary of company clinical data on QT

At the intended therapeutic doses of 5 mg and 10 mg twice daily, asenapine has a small effect on QTc that is less than that seen with quetiapine. Clinically relevant QT prolongation does not appear to be associated with asenapine use. In a dedicated study to assess the effect of asenapine on QT prolongation, exposure-response modeling showed a mild positive effect on the QTc interval. The point estimates of QTcF prolongation associated with mean steady state plasma asenapine Cmax values were less than 5 msec for all doses studied and were less than those for quetiapine (7-8 msec).

Routine ECG monitoring was performed in the complete phase 2/3 program. In the phase 2 short term schizophrenia trials and in one long term schizophrenia trial (25517) ECGs were routinely sent for evaluation to a central reader. For the remainder of the phase 2/3 trials ECGs were sent to a central reader only when QT prolongation was seen on the ECG. Overall incidence of QT prolongation as evaluated by a central reader in asenapine treated subjects was comparable to that seen with placebo (in the short-term trials) and olanzapine (in the long-term trials). In the complete clinical programme no serious adverse events that are associated with QT prolongation were reported (sudden death, cardiac arrest, ventricular fibrillation, or torsade des pointes). Incidence of adverse events possibly related to QT prolongation (such as ECG QT prolonged and syncope) were low and comparable to placebo in the short term trials and comparable to olanzapine in the long term trials.

Reviewer conclusions: *Asenapine was associated with QT prolongation and syncope at comparable levels to Olanzapine. QT prolongation is a labelled effect for olanzapine in both section 4.4 and 4.8 of the SmPC.*

Scientific literature review:

Kotasek, et al (2014): 54-year-old man with a long history of clozapine-resistant schizophrenia presented to hospital following a psychotic relapse. Over the last decade, antipsychotics including aripiprazole, amisupride, ziprasidone and paliperidone have been used to augment his clozapine. At the time of his admission, a routine ECG was conducted revealing a prolonged QTc of 496 ms on the combination of clozapine and quetiapine. Quetiapine, a drug associated with moderate increases in QTc, was immediately ceased and his QTc reduced to 470 ms. After receiving advice from cardiology, asenapine was selected to replace quetiapine for its purportedly low effect on QTc. Within 24 hours of commencing asenapine, an ECG revealed Mr C's QT had risen 30 ms to 500 ms. Asenapine was immediately ceased, and his QTc fell once again, and remained within acceptable limits for the remainder of his admission. Subsequently, olanzapine was used to augment his clozapine with no marked effect on QTc. (Kotasek et al, 2014)

Reviewer comment: *Case assessed using the French Method of causality assessment with outcome Probable due to very suggestive temporality and positive dechallenge.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very suggestive	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C3	**Alternate**	S2
Result	I3	Probable	

Chapel (2009): A parallel design, thorough QTc trial for asenapine in 148 patients with schizophrenia. Patients received asenapine 5 mg twice daily (BID) for 10 days (10d) followed by 10 mg BID (6d),asenapine 15 mg BID (10d) followed by 20 mg BID (6d), quetiapine 375 mg BID (positive control for assay sensitivity; 16d) or placebo (16d). Triplicate 12-lead electrocardiograms and concentration measurements were obtained on day -1 (baseline), 1, 10, and 16 at 8 scheduled times on each day. Results showed that at mean C(max) for all asenapine doses, the **mean QTcF** increase was less than 5 milliseconds, the International Conference on Harmonisation-established threshold for clinical concern. For the positive control Quetiapine, 7- to 8-millisecond prolongation at the dose tested were observed. The corresponding **upper bounds of the 95% confidence intervals were 7.5 milliseconds** and 11.2 milliseconds **for asenapine** and quetiapine, respectively. (Chapel et al, 2009)

Reviewer comment: *this study showed an overall less than 5ms increase in QT by asenapine however the upper bound value was in excess (7.5ms). The study included supra therapeutic doses (15 and 20mg) as recommended by ICH with the largest number of measurements taken at the 5mg and 15mg doses. This study is considered to add to the positive evidence for clinically relevant QT prolonging effect with asenapine.*

Chapel et al (2011): A study on the same data reported in Chapel 2009 this time using a different method to study drug effects on QT interval (the intersection-union test (IUT) (as

recommended in the International Conference on Harmonisation E14 guidance) versus the previous exposure-response (E-R) method analysis results of previous study (Chapel 2009). Although estimates of the time-matched, placebo-corrected mean change in QTc from baseline (ddQTc) at peak plasma concentrations from the E-R analysis ranged from 2 to 5 ms per dose level, the IUT applied to simulated data from the E-R model yielded maximum ddQTc estimates of 7-10 ms for the various doses of asenapine. These results indicate that the IUT can produce biased estimates that may induce a high false-positive rate in individual thorough QTc trials. In such cases, simulations from an E-R model can aid in reconciling the results from the two methods and may support the use of E-R results as a basis for labeling. (Chapel et al, 2011)

Reviewer comment: *this study published a year after authorization shows that using a different method recommended by ICH the estimated QT prolonging effect was of 7-10ms for asenapine. The company states that the IUT method produces biased results yet that method is the method of choice recommended by ICH. This study is considered to add to the positive evidence for clinically relevant QT prolonging effect with asenapine.*

Post-marketing pharmacovigilance data review:

Case 1: Patient with a medical history of cardiac issues taking 10mg sublingual asenapine for unk duration was reported to have a QT interval prolongation from 402ms to 476ms. US-01054554290-2010SP024432

Reviewer comment: *The case has limited information. Using the French Method of causality assessment outcome is Uncertain for the drug-event pair.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 2: 63- year old female patient on concomitant quanaprine, aripiprazole, vitamin C and levothyroxine was started on 10mg twice daily sublingual asenapine. After 1 day of therapy QT interval was reported as prolonged. Patient was already hospitalised and undergoing daily EKGs. US-01054554290-2010SP064016

Reviewer comment: *QT interval prolongation is a know effect of aripiprazole but not of the other drugs. More information would have helped in assessment of this case. The case was assessed using the French Method of causality assessment with outcome Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very Suggestive	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I	Uncertain	

Case 3: Female patient approximately 50 years old, BMI 26.8, height 65 inches with history of smoking cigarettes and marijuana daily was initiated asenapine 5mg once daily sublingual tablet for 3-4 days before presenting with low and irregular BP. EKG performed showed a QTc greater than 500mg. Asenapine was discontinued and QT interval returned to baseline. A family history of prolonged QT interval, hashimoto and hypothyroidism were reported but no family members had cardiac arrythmias or disease. The patient did not have a know underlying cardiac condition or imabalanced electrolytes and did not use any other medication US-01054554290-2010SP061232

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Probable*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very Suggestive	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C3	**Alternate**	S1
Result	I3	Probable	

Case 4: Female patient was initiated on twice daily sublingual asenapine for bipolar disorder and experienced QT prolongation and mouth ulcers causing hospitalisation. Patient had a medical history of cardiac arrhythmias. Therapy was discontinued and symptoms improved. US-01054554290-2011SP018429

Reviewer comment: *Case assessed using the French Method of causality assessment outcome Probable. Ulcerations of the oral mucosa is an expected event with asenapine.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very suggestive	**Symptoms**	Very suggestive
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C3	**Alternate**	S2
Result	I3	Probable	

Case 5: Female patient on asenapine received an EKG which revealed a QT interval over 400. US-01054554290-2011SP026380

Reviewer comment: *QTinterval prolongation is generally accepted to be a reading >440 in Males and >460 in females (debated). However a significant leap from an established baseline can also be drug induced QT interval prolongation. In this case, since no baseline is given and the QT interval prolongation is just >400 then using the French method of causality assessment the outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0

Dechallenge	C1	**Alternate**	S2
Result	I1	Uncertain	

Case 6: 69 year old male patient presented with collapse and respiratory insufficiency. He used quetiapine, sodium valproate and topiramate for 4 days and on the 5th day 20mg asenapine was added. 19days later the patient experience the collapse and respiratory insufficiency and EKG revealed a QT prolongation from 420 to 430ms. The reporting physician did not think this case was related to asenapine as the patient had experienced the same thing in previous years. MAH reports causality as possibly related. DE-01054554290-2011SP036945

Reviewer comment: *QT interval prolongation is an expected event for quetiapine but not for the other drugs. Case assessed using the French Method of causality assessment outcome Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 7: Female patient initiated treatment with 2.5mg asenapine once daily for bipolar disorder. The patient experienced QT prolongation and syncope. A further episode of syncope occured soon after which resulted in a broken arm. Dechallenge information was not available. The event of syncope is listed within the current CCDS of asenapine. The Marketing Authorization Holder assessed the event as possibly related. US-01054554290-2011SP042050

Reviewer comment: *Limited information on dechallenge and concomitant drugs if any. Using the French method of causality assessment the outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S2
Result	I1	Uncertain	

Case 8: 22-year-old female patient weighing 65 kg attempted suicide by administering pipamperone (tablets, oral) 40 dose(s), paracetamol (tablets, oral) 2000 mg diphenhydramine (tablets, oral) 5000 mg, escitalopram oxalate (tablets, oral) 28 dose(s), asenapine 60 mg, prothipendyl hydrochloride 50 dose(s) and hyoscine butylbromide (tablets, oral) 2 dose(s) It was unknown if the patient was routinely prescribed with these medications. The patient experienced increasing somnolence, convulsive seizure, slurred speech, tachycardia (heart rate 110 -<120, systolic hypertension (systolic blood pressure 150 -<160mmHg), "gaze", vomiting, aspiration and increased QTc. Patient's blood circulation was stable (80 per minute). Electrocardiogram showed QTc 500 msec. The patient recovered from the suicide attempt. This case is linked to 20121103892. DE-009507513-1303DEU009283

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 9: 47 year old male patient switched from Clozapine to asenapine maleate 20mg tablet twice daily sublingually for schizophrenia. No concomitant medications reported. A month later the patient experienced loss of consciousness and was admitted to the critical care ward. It was found that he experienced QTc prolongation, urinary retention and seizure. Therapy with asenapine was discontinued and the patient recovered from the events. Reporting physician considers event possibly linked to asenapine. AU-009507513-1302AUS010131

Reviewer comment: *Case assessed using the French Method of causality assessment, outcome Probable. An alternative explanation is that the urinary retention caused some electrolyte imbalance which lead to qt prolongation.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very suggestive	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C3	**Alternate**	S1
Result	I3	Probable	

Case 10: Female patient was on asenapine 10 mg bd and quetiapine fumarate. A routine electrocardiogram showed a prolonged QTc interval of 506. Asenapine was discontinued but QTc prolongation persisted. Thereupon quetiapine fumarate was discontinued and a rechallenge with asenapine maleate was performed. Several ECGs were performed and showed that QTc prolongation resolved. The reporting physician finally assessed the event as not related to asenapine. DE-009507513-1305DEU002639

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Uncertain. QTc prolongation resolved after discontinuation of quetiapine fumarate and after concurrent rechallenge with asenapine.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R-	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 11: 42 year old female patient stopped quetiapine and commenced on asenapine 5mg morning and 10 mg nocte. EKG after 1 week of treatment revealed QTc interval elevated to 474 msec and asenapine maleate was discontinued. Concurrent treatment was with duloxetine (CYMBALTA) at an increasing dose. After stopping asenape, a repeat EKG revealed good QTc at 420ms. No other medications were altered during that period. Reporter assessed event as directly correlated to asenapine. AU-MERCK-1309AUS011946

Reviewer comment: *Case assessed using the French Method of causality assessment. outcome Probable. QT interval prolongation is not an expected effect with duloxetine.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Very suggestive	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C3	**Alternate**	S2
Result	I2	Probable	

Case 12: 52 year old female patient with a history of treatment resistant psychosis was treated with a multitude of medications from 1991 to 1995 including haloperidol, risperidone, paliperidone, thiorizadine, trifluoperazine and clozapine. On all treatments, no cardiac adverse events were experienced. A troponin test on the 18 Feb 2013 showed troponin in normal range (troponin T less than 29 ng/L (normal range: less than 30 ng/L).At the time the main

treatment was Clozaril and risperidone. On 14th May 2014 Clozaril was stopped due to hypersalivation and because was deemed to not be sufficiently effective. The patient received asenapine from 20 May 2014 at a dose of 10 mg. It was advised to slowly titrate the Clozaril but on 20th May the patient ceased abruptly from 400 mg to 0 mg. On 30 May 2014, the dose of asenapine increased to 15 mg and good improvement in mental state was noted on asenapine. This was 19 days before start of cardiac symptoms. On 13 Jun 2014, the patient was commenced on quetiapine XR 50 mg (5 days prior to symptoms). On an unspecified date in Jun (of that year), the patient developed severely impaired left ventricular (LV) systolic function and was diagnosed with myocarditis which was attributed to Clozaril. Treatment with quetiapine was discontinued and LV function improved and by July it was back to normal. In Jun 2014, the patient had dilated cardiomyopathy (ejection fraction: 25 percent)(reported as Clozaril induced by hospital cardiologist). Repeat echocardiograms had returned with significantly improved left ventricular ejection fraction (LVEF) and initial 25 percent reading was postulated to be due to technical error. On 08 Jun 2014, the patient developed nausea, vomiting, diarrhea, weight loss, runny nose and swollen ankles. Treatment with asenapine was discontinued on 08 Jun 2014. On 17 Jun 2014, the patient had a decline in mental state, was unable to sleep, had auditory hallucinations, delusional ideations and anxiety. On 18 Jun 2014, the patient troponin T was 167 ng/L. On 19 Jun 2014, the patient troponin T was 82 ng/L. On 19 Jun 2014, electrocardiogram (ECG) showed sinus tachycardia (heart rate: 122; units and normal range not specified), left anterior fascicular block, non specific T abnormalities in lateral leads, prolonged QT interval (QT interval: 364; units not specified). On 27 Jun 2014, echocardiography showed moderate left ventricular dysfunction compared with echo 8 days ago. On 28 Jun 2014, ECG showed atrial flutter with 4:1 atrioventricular (AV) conduction, right axis deviation, incomplete right bundle branch block, possible anterior infarct, T wave abnormality and consider infero lateral ischemia. On an unknown date in (Jun/ Jul) 2014, the patient was admitted to the hospital and was diagnosed with myocarditis. Treatment with quetiapine was discontinued and treatment with paliperidone was started. On an unknown date in (Jun/ Jul) 2014, QTc increased with increasing doses of paliperidone. On 30 Jun, treatment with paliperidone was ceased. On 04 Jul 2014, ECG showed T wave inversion (compared to old ECG), QTc interval prolonged (QTc: 510 ms and 514ms). On 10 Jul 2014, the ECG showed T wave abnormality (consider lateral ischemia) and QT was still prolonged. On 10 Jul 2014, the patient troponin T was less than 29 ng/L. On 10 Jul 2014, hemoglobin was 112g/L (normal range: 115 to 155 g/L), mean cell Hb count was 309 g/L (normal range: 310 to 360 g/L), platelet count was 488 x 10 E9/L (normal range: 150 to 450 x 10 E9/L), white cell count was 11.9 x 10 E9/L (normal range: 4.0 to 11.0 x 10 E9/L), neutrophils was 9.10 x 10 E9/L (normal range: 1.80 to 7.50 x 10 E9/L). On 10 Jul, the patient experienced decline in mental state on olanzapine and lorazepam. On 15 Jul 2014, hemoglobin was 110g/L, mean cell Hb count was 385 g/L, platelet count was 465 x 10 E9/L, white cell count was 16.6 x 10 E9/L, neutrophils was 12.91 x 10 E9/L, monocyte was 0.98 x 10 E9/L (normal range: 0.20 to 0.80 x 10 E9/L). On 16 Jul 2014,hemoglobin was 110 g/L, mean cell Hb count was 309 g/L, sodium was 135 mmol/ L(normal range: 137 to 145 mmol / L), glucose was 6.20 mmol/L (normal range:3.2 to 5.5 mmol/ L), urea was 2.3 mmol/ L (normal range: 2.70 to 8.0 mmol/ L),urate was 0.52 mmol/ L (normal range: 0.15 to 0.45 mmol/ L), phosphate was 1.64 mmol/ L (normal range: 0.65 to 1.45), total protein was 63 g/L (normal range: 65 to 85 g/L). On 21 Jul 2014, hemoglobin was 108 g/L, mean corpuscular hemoglobin (MCH) was 26.9 pg (normal range: 27.0 to 33.0 pg), mean cell Hb count was 309 g/L, chloride was 99 mmol/ L (normal range: 100 to 109 mmol/L), anion gap was 18 mmol/ L (normal range: 7 to 17 mmol/ L), glucose was 5.9 mmol/L, urate was 0.58 mmol/ L, phosphate was 1.48 mmol/ L. On 21 Jul 2014,echocardiography was performed (cardiologist impression not provided). On 24 Jul 2014, ECG showed normal sinus rhythm, normal ECG. On 06 Aug 2014,hemoglobin was 107 g/L, packed cell volume was 0.34 L /L (normal range: 0.35 to 0.45), monocytes was 0.84 x 10

E9/L (normal range: 0.20 to 0.80 x 10 E9/L),chloride was 95 mmol/ L, anion gap was 24 mmol/ L, glucose was 6.2 mmol/L,urate was 0.46 mmol/ L, albumin was 31 g/L (normal range: 34 to 48 g/L), total protein was 62 g/L. On an unknown date, it was reported that, the patient commenced on various cardio medications (perindopril 5 mg, spironolactone 25mg, carvedilol 12.5 mg BD and furosemide 40 mg) which had subsequently affected the lithium levels. It was reported that lithium had to be ceased (which the patient responded well to) and commenced on valproate. On an unknown date in Jul, the patient was non compliant with olanzapine. On an unknown date in Jul treatment with olanzapine discontinued (ceased). It was reported that the Clozaril had some benefit with mental state. The event myocarditis was reported as serious (hospitalization). The outcome of the event left ventricular (LV) systolic function was complete recovery. The causality of the events impaired left ventricular (LV) systolic function and myocarditis was suspected to Clozaril (developed severely impaired LV systolic function and was diagnosed with myocarditis which was attributed to Clozaril however it is unlikely that Clozaril was the cause of impaired LV systolic function as it was discontinued well before the cardiomyopathy was diagnosed. The causality of the event cardiomyopathy was suspected to quetiapine (more likely that quetiapine was the culprit given that cardiomyopathy developed soon after it was started) and not reported for the remaining suspects. The causality of the event dilated cardiomyopathy was suspected to quetiapine (likely caused this). The causality of the event QTc increased was suspected to paliperidone and not reported for the remaining suspects. Follow up report received from quality assurance department on 07 Jul added suspects (asenapine, quetiapine, lorazepam, paliperidone and olanzapine). AU-EMA-20141229-ssharmap-172040036.

Reviewer comment: *Temporality positive for asenapine administration started 19 days prior to events and quetiapine started 5 days prior to events. Concomitant medications were all taken in the past without reporting of adverse cardiac events. When asenapine and quetiapine were stopped test parameters for cardiac function improved steadily. This case shows some evidence to an additive detrimental effect of these two drugs when co administered. French causality assessment for asenapine-ADR pair is Possible.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C2	**Alternate**	S2
Result	I3	Possible	

Case 13: Female patient started therapy with asenapine sublingual tablet, 5 mg. Co-suspect therapy included fluoxetine. The patient experienced dizziness and therapy with asenapine and fluoxetine were stopped. The patient was hospitalized, her electrocardiogram QT interval was found to be prolonged (525 sec), and potassium levels were also reported to be increased. AU-009507513-1501AUS009043

Reviewer comment: *QT interval prolongation is an expected event with fluoxetine but a contribution from asenapine cannot be excluded. French causality assessment for asenapine-ADR pair is Uncertain*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case14: Prolongation of QT interval in patient of unknown age and gender after taking asenapine. No further information US-009507513-1504USA004263

Reviewer comment: *Case not assessable*

Case 15: Patient of unk gender started therapy with asenapine 10 mg daily. Other suspect therapies included quetiapine fumarate of dose 300 mg daily started on 01-DEC-2014. Concomitant therapies included ascorbic acid, coloxyl, cranberry, enoxaparin sodium, methenamine hippurate, lithium carbonate, acetaminophen, pregabalin and senna. On 11-DEC-2014, the patient experienced QT prolongation of 617 units (MET (medical emergency team was called due to tachycardia) (medically significant). The patient was treated with decreased quetiapine fumarate. The patient's initial blood pressure (BP) was 110/60 (unspecified units) and manual pressure was 72/50 (unspecified units). As of 30-DEC-2014, daily eletrocardiogram (ECG) was recommended and patient was advised to continue quetiapine fumarate if QT was less than 520. Patient was also advised to proceed with electro convulsive therapy. The patient was in a very severe psychotic state. Action taken with asenapine maleate was not reported. The outcome of electrocardiogram QT prolonged was unknown. The reporter considered electrocardiogram QT prolonged to be possibly related to asenapine maleate. AU-MERCK-1504AUS018091

Reviewer comment: *The reporter considered electrocardiogram QT prolonged to be possibly related to asenapine maleate. Little is known on temporality and dechallenge. The French causality assessment outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 16: 66 year old female patient prescribed asenapine 5 mg orally twice daily started on 30-JUL-2015 for schizophrenia. On 11-AUG-2015, the patient experienced QTc interval prolongation at 508 (unit not provided). Patient's medical history included cholesterol, hypertension, hyperthyroidism and heart failure. Co-suspected drugs comprised of:

olanzapine 10 mg per oral at bedtime (in decreasing doses), venlafaxine hydrochloride 150 mg per oral once daily (in decreasing doses) from 2008 to 2015 for schizophrenia. Also salmeterol xinafoate, bisoprolol fumarate and furosemide. AU-STADA-097331

Reviewer comment: *QTc prolongation is expected for olanzapine and venlafaxine, French causality assessment outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Case 17: A consumer report describing occurrence of occasional seizure, prolonged QT intervals, lost 80 pounds, sores under her tongue, ulcers under her tongue, irritation under tongue and loss of appetite in 45 year old female patient after taking asenapine maleate for treatment of schizophrenia. Relevant medical history included diabetes and a heart arrhythmia. The patient also had an allergy to ciprofloxacin and a history of prior clozapine use that caused complete "havoc on her life". Concomitant medications included gabapentin, heart arrhythmia medications and diabetes medications. While on Asenapine the patient reported experiencing an occasional seizure, prolonged QT intervals, loss of 80 pounds, had a loss of a appetite, and sores, ulcers and irritation under her tongue. The patient considered the weight loss to be a good thing. Despite the events however, asenapine maleate continued but patient remained under monitoring for QT prolongation. US-MERCK-1403USA008339

Reviewer comment: *French causality assessment outcome is Uncertain*

Causality Assessment (French Method)			
Chronological criteria		**Semiological criteria**	
Challenge	Compatible	**Symptoms**	Compatible
Rechallenge	R0	**Lab Test**	L0
Dechallenge	C1	**Alternate**	S1
Result	I1	Uncertain	

Active substance	Bradford-Hill criterium	Assessment
ASENAPINE	Strength of association	4.60 PRR, 1 Literature case and 17 ADR Case reports Outcome of the cases was as Probable in 5 cases, Possible in 2 cases 10 cases were uncertain due to confounding factors. 3 articles directly relevant to QT effects with asenapine were retrieved from Pubmed.
	Biological Plausibility	Asenapine prolonged QT interval in clinical studies and blocked the hERG channel, *in vitro* laboratory models. QTc prolongation was seen in animal *in vivo* experiments.
	Biological gradient	Whether increased blockade of I_{Kr} occurs at higher doses is not apparent.
	Experimental evidence and temporality	Of the 17 cases assessed, all had a temporal relationship between the events and the initiation of treatment. Some cases had sparse information and others were confounded by other drugs or underlying cardiac conditions (uncertain cases) However in 2 cases asenapine was the only suspect drug and in 5 cases decreases in the dosage or stopping treatment with asenapine resolved the symptoms (positive dechallenge).
	Consistency	2 cases had the same profiles, ie. QT prolongation plus mouth ulcers. Mouth ulcers is an expected adverse event with asenapine. Physicians and patients have reported the same event. Reports originate from different countries in EU and non EU with possibly different prescribing patters. Signal involves both healthy volunteers (experimental evidence) and postmarketing evidence.
	Specificity	In preclinical data asenapine was found to bind the human ether-a-go-go-related gene (hERG) potassium channel, as well as affects AP duration which provides a plausible mechanism for QTc interval prolongation.
	Analogy	Other antipsychotics bind to hERG, which provides an analogy for asenapine causing clinically relevant QTc interval prolongation.
Overall assessment	*In the Eudravigilance database the association between asenapine and QT interval prolongation was disproportionally reported for this drug over others. Literature and case review supports the relation, and preclinical data demonstrates a mechanism of action. While this event is already listed in section 4.8 with a frequency uncommon a conflicting statement in 4.4 exists where it is*	

	stated that Clinically relevant QT prolongation is not expected with this product. The proposal therefore is to remove this 4.4 wording from the SmPC.
Benefit Risk	***The benefit risk balance of this product remains positive***

Appendix 3:
Mirabegron

Malta, January2017

Signal Description Message

From	To	Copy to
Amy Tanti	Post-Licensing Directorate	Professor John J Borg

Subject

Medicinal product	Mirabegron (Betmiga® 25 mg and 50mg tablets)
Signal (MedDRA term)	Electrocardiogram QT interval prolonged

Priority Grade Proposal:

Important risk

Summary

Imputability Score	**Number of case**
I4-Highly Probable	1
I3-Probable	1
I2-Possible	6
I1-Uncertain	6
I0 -Unlikely	0

Signal characteristics

Source (database, literature…)	Eudravigilance database, medical literature, company clinical and pre-clinical data
Number of reports	15 total, 14 assessable 1 EU, 13 Non-EU. Additional data from pre-clinical submission, clinical studies and literature.
Expectedness	No
Seriousness	Yes Drug induced QT interval prolongation predisposes to arrhythmias, including the lethal Torsade de Pointes.
Statistics (if available, e.g. PRR, IC, confidence interval…)	

Reaction PT	PRR (-)	PRR	PRR (+)	Static PRR Analysis - CHI^2
Electrocardiogram QT prolonged	0.637196	1.223742	2.35021016	0.368798769

Mirabegron: Betmiga® 25mg and 50mg prolonged-release tablets

Mechanism of action: Mirabegron relaxes bladder smooth muscle thereby enhancing urine storage function by stimulating beta 3-adrenoceptors in the bladder.

Date EU approval: 20 December 2012

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Availability in MT: not available on the GFL, available in private sector.

Currently authorised SmPC wording:

Section	Wording
4.3 Contraindications	*Not listed*
4.4 Warnings	*<u>Patients with congenital or acquired QT prolongation</u>* *Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.*
4.5 Interactions	*Not listed*
4.8 List of ADRs	*Not listed*
5.0 Pharmacology	*<u>Effect on QT interval</u>* *Betmiga at doses of 50 mg or 100 mg had no effect on the QT interval individually corrected for heart rate (QTcI interval) when evaluated either by sex or by the overall group.*

▼This medicinal product is subject to additional monitoring.

Summary of company preclinical data

In vitro Mirabegron, at concentrations up to 30 mcmol/L, did not inhibit the hERG current (IKr) in human embryonic kidney cells (HEK293 cells) stably transfected with the hERG channel. In a confirmatory hERG assay study, mirabegron at a concentration of 30 mcmol/L showed a slight inhibitory effect (14.7%) on the hERG current. As this effect was observed at concentrations that were 657-fold higher than the Cmax, observed at the Maximal Recommended Human Dose (MRHD), it was concluded that these findings were not of clinical significance. Mirabegron had no effect on action potential in isolated guinea pig papillary muscle, nor did it affect the QTc interval in cynomolgus monkeys. Of five human plasma metabolites (M5, M11, M12, M14, and M16) of mirabegron, the major metabolites M11 and M12 had no effect on hERG current or action potential in isolated guinea pig papillary muscle. M5, M14, and M16 revealed great differences between IC50 or inhibitory concentrations of hERG current and Cmax, of each metabolite at the maximum human dose. M5 and M16 showed statistically significant prolongation of APD30 or APD90 in isolated guinea pig papillary muscle; however, the change was mild (6.1% at most) and caused no change in APD30-90, which corresponded to the late repolarization phase of action potential in cardiac muscle. Mirabegron and its five most abundant human plasma metabolites showed no inhibitory effect on slow delayed rectifier potassium current (IKs), which has been believed to be a factor affecting the late repolarization phase of action potential of cardiac muscle, as is the hERG current. Furthermore, neither mirabegron nor its five human plasma metabolites (M5, M11, M12, M14, and M16) prolonged QT interval or action potential duration, or showed any arrhythmogenic effects in arterially perfused canine ventricular wedge preparation.

Oral administration of mirabegron to cynomolgus monkeys at doses up to 100 mg/kg did not prolong the QTc interval using Bazzetts formula (38.4-fold higher than the human equivalent dose). In the 52-week repeated dose study in monkeys, oral administration of mirabegron at a dose of 30 mg/kg/day also had no effect on the QTc interval in males but female monkeys at this same dose did show a significant QTc interval prolongation only at the 39 week time point. This finding was absent when the QT interval was corrected using the Matsunaga formula. The company refers to papers showing that the Matsunaga method was a more appropriate correction method for use in dogs, in that it has less over- or under-correction for heart rate [Matsunaga et al, 1998; Miyazaki 2002]. In dogs, QTcF interval prolongation was observed in both male and female dogs at a dose of 10 mg/kg (12.7- and 8.9-fold higher than the clinical exposure at the MRHD in males and females respectively) on day 1 of dosing but not on day 14 (systemic exposure 25.1- and 13.8-fold the human exposure at MRHD for males and females, respectively

An evaluation of the potential for mirabegron or its five most abundant human plasma metabolites (M5, M11, M12, M14, and M16) to alter ion channel conductance was performed. Major metabolites M11 and M12 had no effect on hERG channel current or guinea pig papillary muscle action potential. Minor metabolites M5 and M16 inhibited the hERG channel current with a 50% inhibitory concentration (IC50) of 21 and 31 mcmol/L,respectively. These concentrations were 1955- and 2907-fold, higher than the clinical Cmax, at the MRHD. Minor metabolite, M14, achieved only a 17.3% inhibition of the hERG channel current at the highest concentration tested, 30 mcmol/L (2553-fold higher than the clinical Cmax). In addition, the effect of mirabegron and its metabolites on two additional potassium currents, the slow delayed rectifier current (IKs) and transient outward potassium current (Ito) were determined. Neither mirabegron nor any of the five human plasma metabolites tested inhibited the IKs or Ito currents at concentrations up to 10 mcmol/L. These data showed that neither mirabegron nor the five most abundant human plasma metabolites tested inhibited potassium mediated membrane repolarization, at clinically relevant concentrations.

Mirabegron and minor metabolite, M16 at a concentration of 10 mcmol/L, inhibited the sodium current by 48.5% and 10.5%, respectively. In addition, mirabegron and M16 also inhibited the high threshold calcium current, ICa,L by 15.3, and 8.8% respectively at a concentration of 10 mcmol/L. For both ion channels, the concentrations that were weakly inhibitory were 219- and 938-fold the clinical Cmax, u for mirabegron and M16, respectively.

As such, the company concluded that neither mirabegron nor the five most abundant human plasma metabolites tested had an effect on cardiomyocyte depolarization or repolarization at clinically relevant concentrations. Support for this conclusion was drawn from the observation that mirabegron did not alter the action potential duration or rate of depolarization of guinea pig papillary muscles in vitro. M5 and M16 significantly prolonged APD30 or APD90 in isolated guinea pig papillary muscles;

however the change was at most 6.1%, and caused no change in APD30-90 which corresponds to the late repolarization phase of action potential in cardiac muscle. Finally, neither mirabegron nor the five human plasma metabolites tested prolonged the QT interval, action potential duration, or ventricular transmural dispersion of repolarization in arterially perfused dog left ventricular wedge preparations. They also did not demonstrate arrhythmogenic potential in this same model. Taken together, the ion channel inhibition studies, action potential duration studies, and isolated perfused ventricular wedge studies indicate that mirabegron and its five metabolites tested will not have a major discernable effect on the sodium, potassium, or calcium ion conductance at clinically relevant concentrations.

Reviewer conclusions: *The company has observed that at much higher doses than those expected clinically, QTc interval prolongation in both dogs and monkeys is expected using the QTc correction method by Bazzett. Mirabegron metabolites M5 and M16 inhibited the hERG channel current with a 50% inhibitory concentration (IC50) of 21 and 31 mcmol/L,respectively at concentrations of 1955- and 2907-fold, higher than the clinical Cmax, at the maximum recommended human dose. Metabolite M14, inhibited 17.3% of the hERG channel current at the highest concentration tested, 30 mcmol/L (2553-fold higher than the clinical Cmax). Inhibitory effects on hERG in pig papillary muscles occurred again only at high concentrations in vitro. These tests show a biological plausibility for a QT prolonging effect in humans, via hERG inhibition, with mirabegrons M5 and M16 and M14 metabolites; however this would not be expected to occur at clinically relevant concentrations.*

Summary of company clinical data

Effect on QT Intervals of the Electrocardiogram

A dedicated thorough QT study showed that, according to ICH E14 criteria, mirabegron did not cause individually corrected QT interval (QTcI) prolongation at the proposed therapeutic dose of 50 mg or the supratherapeutic dose of 100 mg. At both doses, the upper bound of the 1-sided 95% CI of corrected QT interval (QTc) interval did not exceed 10 msec at any time.
At a supratherapeutic dose of mirabegron 200 mg, a QTc prolongation, according to ICH E14 criteria, was observed in female but not male volunteers. In females at this dose, the upper bound of the 1-sided 95% confidence interval exceeded 10 msec between 0.5 and 6 hours, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the 1-sided 95% CI 13.44 msec). In males, the upper bound of the 1-sided 95% CI of the QTc interval did not exceed 10 msec at any time point. The increased QTc effect in female volunteers was consistent with their higher mean Cmax and AUCtau of mirabegron compared to male volunteers. At the 200 mg dose, mean Cmax and AUCtau were approximately 8.4- and 6.5- fold higher, respectively, relative to the proposed therapeutic dose of 50 mg. In the event of a drug-drug interaction between mirabegron and strong inhibitors of CYP3A, mirabegron plasma exposure with 50 mg will not reach exposures at which QTc interval prolongation was demonstrated. Likewise, in patients with severe renal or moderate hepatic impairment, mirabegron plasma exposure with 25 mg will not reach exposures associated with QTc interval prolongation.

Reviewer conclusions: *At a supratherapeutic dose of 200mg QTc prolongation was observed in female but not male volunteers. The company states that with a drug-drug interaction or in patients with kidney and renal impairment they do not expect that mirabegron will reach the levels of exposure associated with QT prolongation. The company does not take into account in their assumptions, the imperfect use of drugs by patients or possible accumulation effects of this drug though its long half-life.*

PK-QTc Interval Analyses

The relationship between mirabegron plasma concentration and difference in baseline adjusted QTc from placebo (ddQTcI) was characterized through a linear mixed effects model using data from the above mentioned through QT study. In female and male volunteers, the slope of the ddQTcI versus mirabegron concentration was positive and significant, suggesting that an increase in mirabegron concentration produced an increase in ddQTcI. The results were similar in the overall population (both female and male volunteers).
Data from through QT study were also analyzed using population PK and concentration-response modeling. Exploratory graphical analysis also showed that the overall magnitude of effect for mirabegron on QTcI increased with increasing mirabegron concentration.

Reviewer conclusions: *An increase in mirabegron concentration produced an increase in ddQTcI in both females and males demonstrating a clear biological gradient for drug concentration and adverse event.*

Scientific literature

Katoh et al (2016) Real-world cardiovascular assessment of mirabegron treatment in patients with overactive bladder and concomitant cardiovascular disease: Results of a Japanese post-marketing study.

Method: Participants had overactive bladder, a history of/coexisting cardiovascular disease and a 12-lead electrocardiogram carried out ≤7 days before initiating 4 weeks of mirabegron treatment. Patients with "serious cardiovascular disease" (class III or IV on the New York Heart Association functional classification and further confirmed by expert analysis) were excluded. Patient demographics, physical characteristics and cardiovascular history were recorded. After 4 weeks, patients underwent another electrocardiogram. Incidence of cardiovascular adverse drug reactions and change from baseline in electrocardiogram parameters (RR, PR, QRS intervals, Fridericia's corrected QT and heart rate) were assessed. Results: Of 316 patients registered, 236 met criteria and had baseline/post-dose electrocardiograms: 61.9% male; 60.2% aged ≥75 years; 93.6% with coexisting cardiovascular disease, notably, arrhythmia (67.8%) and angina pectoris (19.1%). Starting mirabegron daily doses were 25 mg (19.9%) or 50 mg (80.1%). The incidence of cardiovascular adverse drug reactions was 5.51%. After 4 weeks, the mean heart rate increased by 1.24 b.p.m. (statistically significant, but clinically acceptable as per previous trials). No significant changes were observed in PR, QRS or Fridericia's corrected QT. No significant correlations in the total population or age-/sex-segregated subgroups were observed between baseline Fridericia's corrected QT and change at 4 weeks. No correlation for heart rate versus change from baseline heart rate with treatment was observed. Conclusions: Mirabegron was well tolerated in real-world Japanese patients with overactive bladder and coexisting cardiovascular disease. No unexpected cardiovascular safety concerns were observed. (Katoh et al, 2016)

Reviewer conclusions: *The authors in this abstract cite a cardiovascular adverse event of 5.51% without further characetrisation. Full text was not accessible at time of review. Only arrhythmia and angina pectoris patients are included.*

Nomura et al (2016) Pharmacokinetic drug interaction study between overactive bladder drugs mirabegron and tolterodine in Japanese healthy postmenopausal females.

Mirabegron, the first selective β_3-adrenoceptor agonist for the treatment of overactive bladder (OAB), inhibits cytochrome P450 isozyme CYP2D6. This study was performed in Japanese healthy postmenopausal female volunteers to assess any pharmacokinetic drug interaction between mirabegron and tolterodine, another OAB drug and a sensitive substrate of CYP2D6. Tolterodine 4 mg was orally administered from Days 1-7 and co-administered with mirabegron 50 mg from Days 8-14. Mirabegron 50 mg increased maximum concentration (C_{max}) and area under the concentration-time curve from zero to 24 h after dosing (AUC_{24h}) of tolterodine by 2.06-fold (90% confidence interval [CI] 1.81, 2.34) and 1.86-fold (90% CI 1.60, 2.16), respectively, and increased C_{max} and AUC_{24h} of the metabolite 5-hydroxymethyl tolterodine by 1.36-fold (90% CI 1.26, 1.47) and 1.25-fold (90% CI 1.15, 1.37), respectively. This suggested a weak pharmacokinetic drug interaction between mirabegron and tolterodine. Mean change from baseline of Fridericia's QT correction formula (ΔQTcF) was slightly higher on Day 14 than on Day 7. No subject had QTcF >480 msec or ΔQTcF >60 msec. All the treatment-emergent adverse events were mild. Mirabegron 50 mg was considered to be safe and well tolerated when coadministered with tolterodine 4 mg in healthy postmenopausal female volunteers. (Nomura et al, 2016)

Reviewer conclusions: *These authors take an unconservative approach to QTc prolongation. Well known perpatrators of QT interval such as the class III antiarrythmics cause delta changes of aprox 30ms, yet authors are reassured that the interaction produces a delta of not larger than 60ms. It is unclear whether any of the women had heart disease. Full text was not accessible at time of review.*

Nozawa et al (2016) Safety and Effectiveness of Mirabegron in Patients with Overactive Bladder in a Real-World Clinical Setting: A Japanese Post-Marketing Study

Objectives: To examine prescribing patterns, adverse drug reaction (ADR) incidence, and treatment effectiveness of mirabegron. Methods: Full medical histories, including prior/concomitant drug use, were collected before initiating mirabegron treatment. After 12 weeks mirabegron, physicians assessed ADR incidence and treatment effectiveness. Residual urine volume was assessed and patients completed the Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom Score-Quality of Life (I-PSS QoL) surveys at Baseline and 12 weeks. Data were collected between April 2012 and July 2014. Results: Of 9795 OAB patients (46.8% male; 80.8% ≥65 years), 71.7% had coexisting disease [notably benign prostatic hyperplasia (BPH, 32.4%), hypertension (31.9%), and diabetes mellitus (9.4%)] and 53.4% reported concomitant drug use (27.8% α1-antagonists, 6.3% anticholinergics). The incidence of total ADRs was 6.07% [including constipation (0.97%), thirst (0.47%), and dysuria (0.44%)], of serious ADRs, 0.21%, of cardiovascular ADRs, 0.48% and of urinary retention, 0.31%. Incidence of total ADRs in patients with concomitant cardiovascular disease was 10.09% and of those related to urinary retention in men with untreated BPH, 0.88%. After 12 weeks treatment, physicians judged mirabegron as ''effective'' in 80.7% of patients, 63.6% of patients achieved the threepoint minimal clinically important change from Baseline in the mean OABSS, and the I-PSS QoL decreased significantly from Baseline (-2.1 ± 1.77; $P < 0.001$). Conclusions: In the clinical setting, mirabegron is well tolerated, with no unanticipated ADRs, and is an effective treatment for Japanese patients with OAB. (Nozawa et al, 2016)

Reviewer conclusions: *In the safety group, 674 patients (6.9%) had concurrent CV disease. The total incidence of ADRs in this population was 10.09%, compared with 5.79% in the remaining 8965 patients without concurrent CV disease. This study shows that patients with concurrent CV disease who take mirabegron are at higher risk of ADRs when compared to other patients. CV ADRs reported during the study period included palpitations (17 events), hypertension (nine events), tachycardia (five events), increased blood pressure (four events), hot flush and cardiac failure (three events each), arrhythmia (two events), supraventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, heart rate increased, deep vein thrombosis, pallor, and N-terminal prohormone brain natriuretic peptide increased. This study also had a number of drop outs 873/9795 due to none study visit and due to ADR. The authors did not disclose what the ADRs leading to drop outs were and so higher rates of ADRs than cited are likely.*

Balachandran (2015) The risk and severity of developing symptomatic palpitations when prescribed mirabegron for overactive bladder.

Method: A consecutive cohort of patients with OAB was studied between February 2013 and June 2014. Patients were prescribed mirabegron 50mg daily and outcomes assessed at 6 weeks. Patients with known cardiac arrhythmias were excluded. In patients who developed palpitations, a detailed account of their symptoms and medical history were documented and a 12-lead electrocardiogram (ECG) was performed to assess heart rate, QT interval and the presence of any persisting arrhythmia was conducted. Results: 279 patients were started on mirabegron. Eight patients (2.9%) reported palpitations whilst taking the drug. Two patients with a history of palpitations with no history of prolonged QT interval or arrhythmia on ECG developed worsening palpitations. The QTc was prolonged in two patients at 0.458 and 0.441s (QTc <420). Three patients developed chest pain or tightness. The palpitations resolved once therapy was stopped and did not result in serious adverse events such as hospitalisation. Conclusion: Palpitations in an unselected population have a similar incidence to that demonstrated in previous drug trials. Palpitations may be associated with a worsening of cardiovascular dysfunction (Balachandran and Duckett, 2015).

Reviewer conclusions: *This study demonstrates some evidence that mirabegron prolongs the QT interval with clinical symptoms in some patients. Known cardiac arrhythmia patients were excluded which could mean that effects may have been bigger in these patients.*

Yamaguchi et al (2015) Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study).

Method: open-label, phase IV study enrolled patients aged ≥20 years with OAB, as determined by an OAB symptom score (OABSS) total of ≥3 points and an OABSS Question 3 score of ≥2 points, who were being treated with solifenacin at a stable dose of 2.5 or 5 mg once daily for at least 4 weeks. Study duration was 18 weeks, comprising a 2-week screening period and a 16-week treatment period. Patients meeting eligibility criteria continued to receive solifenacin (2.5 or 5 mg once daily) and additional mirabegron (25 mg once daily) for 16 weeks. After 8 weeks of treatment, the mirabegron dose could be increased to 50 mg if the patient's symptom improvement was not sufficient, if he/she was agreeable to the dose increase, and the investigator judged that there were no safety concerns. Safety assessments included adverse events (AEs), laboratory tests, vital signs, 12-lead electrocardiogram, QT corrected for heart rate using Fridericia's correction (QTcF) interval and post-void residual (PVR) volume. Efficacy endpoints were changes from baseline in OABSS total score, OAB questionnaire short form (OAB-q SF) score (symptom bother and total health-related quality of life [HRQL] score), mean number of micturitions/24 h, mean number of urgency episodes/24 h, mean number of urinary incontinence (UI) episodes/24 h, mean number of urgency UI episodes/24 h, mean volume voided/micturition, and mean number of nocturia episodes/night. Patients were instructed to complete the OABSS sheets at weeks -2, 0, 8 and 16 (or at discontinuation), OAB-q SF sheets at weeks 0, 8 and 16 (or at discontinuation) and patient voiding diaries at weeks 0, 4, 8, 12 and 16 (or at discontinuation). Results: Overall incidence of drug-related treatment-emergent AEs (TEAEs) was 23.3%. Almost all TEAEs were mild or moderate. The most common TEAE was constipation, with similar incidence in the groups receiving a dose increase to that observed in the groups maintained on the original dose. Changes in PVR volume, QTcF interval, pulse rate and blood pressure were not considered to be clinically significant and there were no reports of urinary retention. Significant improvement was seen for changes in efficacy endpoints from baseline to end of treatment (EOT) in all groups (patients receiving solifenacin 2.5 or 5 mg + mirabegron 25 or 50 mg). Conclusion: Add-on therapy with mirabegron 25 mg once daily for 16 weeks, with an optional dose increase to 50 mg at week 8, was well tolerated in patients with OAB treated with solifenacin 2.5 mg or 5 mg once daily. There were significant improvements from baseline to EOT in OAB symptoms with combination therapy with mirabegron and solifenacin. Add-on therapy with mirabegron and an antimuscarinic agent, such as solifenacin, may provide an attractive therapeutic option. (Yamaguchi et al, 2015)

Reviewer conclusions:
In this study, the mean change in the QTcF interval from baseline to End of Treatment EOT was 4.3ms for the solifenacin 2.5 mg + mirabegron 25 mg group, 3.4ms for the solifenacin 2.5 mg + mirabegron 50 mg, 2.0ms for the solifenacin 5 mg + mirabegron 25 mg, and and 2.2 ms for the solifenacin 5 mg + mirabegron 50 mg groups, respectively. Therefore in this study, the higher the doses of solifenacin (solifenacin is expected to prolong the QT interval according to its SmPC) and mirabegron, the lower the mean length of the QT interval at end of treatment. This is conflicting to other evidence seen so far however this could be partly explained because the authors quote mean increases of QTc. At EOT, absolute QTcF intervals of >450 ms were noted in five patients (2.4%), but there were no patients with absolute QTcF intervals of >480 ms. Increases in the QTcF interval of between >30 ms and ≤60 ms from baseline to EOT were seen in three patients (1.4%) but there was no patient with a >60 ms increase. Patients with any abnormal electrocardiogram (ECG), long QT syndrome or serious heart disease where excluded from this study. This study adds evidence that mirabegron can prolong the QT interval.

Sanford (2013) Mirabegron: a review of its use in patients with overactive bladder syndrome.

Mirabegron is a β3-adrenergic receptor agonist approved in several countries for the symptomatic treatment of adults with overactive bladder syndrome. In three 12-week, randomized, double-blind, placebo-controlled, multinational trials in patients with overactive bladder syndrome, oral mirabegron 25 or 50 mg once daily significantly reduced the adjusted mean number of

incontinence episodes per 24 h (in patients with incontinence at baseline) and the adjusted mean number of micturition episodes per 24 h (in full trial populations) [coprimary endpoints]. Across trials, mirabegron 50 mg once daily also consistently significantly reduced urgency episodes and increased the volume of urine voided per micturition, generally in association with improved health-related quality of life (HR-QOL) and treatment satisfaction. Based on descriptive analyses from a 12-month trial, once-daily mirabegron 50 mg and tolterodine extended-release (ER) 4 mg were both efficacious in reducing urinary symptoms and improving HR-QOL. Mirabegron was generally well tolerated in the trials. Over 12 weeks, the adverse event rate with mirabegron 50 mg once daily was similar to that with placebo. During 12 months of treatment, 2.8 % of mirabegron 50 mg once daily recipients reported dry mouth compared with 8.6 % with tolterodine ER 4 mg once daily recipients. Mirabegron 50 mg once daily carries a low risk of QT interval prolongation. Thus, mirabegron is an efficacious new treatment for overactive bladder syndrome with a favourable tolerability profile. (Sanford, 2013)

Reviewer conclusions: *In this paper, the authors acknowledge a risk (low) of QT interval prolongation with Mirabegron.*

Malik et al (2012) Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study.

Method: four-arm, parallel, two-way crossover study, double-blind and placebo- and active (moxifloxacin)-controlled. After 2 baseline ECG days, subjects were randomized to one of eight treatment sequences (22 females and 22 males per sequence) of placebo crossed over with once-daily (10 days) 50, 100, or 200 mg mirabegron or a single 400-mg moxifloxacin dose on day 10. In each period, continuous ECGs were recorded at two baselines and on the last drug administration day. Results: The lower one-sided 95% confidence interval for moxifloxacin effect on QTcI was >5 ms, demonstrating assay sensitivity. According to ICH E14 criteria, mirabegron did not cause QTcI prolongation at the 50-mg therapeutic and 100-mg supratherapeutic doses in either sex. Mirabegron prolonged QTcI interval at the 200-mg supratherapeutic dose (upper one-sided 95% CI >10 ms) in females, but not in males. (Malik et al, 2012)

Reviewer conclusions: *In this study a crossover parallel 4 arm trial design was used. While this crossover design has the advantage of a smaller sample size, this should be used only for drugs with a short half-life. In this paper, the authors quote an 'effective half life of 19hrs'for mirabegron. The effective half life is a pharmacokinetic concept developed to take into account drug accumulation but this concept has not been widely accepted.* (Boxenbaum and Battle, 1995) *According to the SmPC of mirabegron, the terminal half-life is 50hrs. This means that a large washout period would have been required to eliminate any carryover effects. If a large washout period is required, hence a longer time between ECGs a substantial spontaneous variation in the QTc interval may occur in the same individual over the study period of weeks. In this study by Malik, the primary study outcomes were derived from within-subject comparisons. Carryover effects which could effect changes from baseline QTc after adjusting for placebo differences is therefore a theoretical possibility.*
Nonetheless the following results with respect to QT change where observed from this study; At the 50-mg therapeutic dose, mean ΔΔQTcI was below 5ms at all time points and the upper bound of the one-sided 95% CI did not exceed 10ms for either sex. At the supratherapeutic 100-mg dose, the upper bound of the onesided 95% CI did not exceed 10ms for either sex. Mean ΔΔQTcI for 100mg was above 5ms at various time points for females but below 5ms at all time points for males. For the supratherapeutic 200-mg dose, the upper bound of the one-sided 95% CI was above 10ms from 0.5 to 6h (except for 1h) and at 10h for females, whereas it did not exceed 10ms at any time point for males. Mean ΔΔQTcI was above 5ms at most time points for both sexes. For 50mg mirabegron, the largest mean ΔΔQTcI (upper bound of the one-sided 95% CI) was 4.49ms (6.81ms) in females at 3.5h, and 2.96ms (5.00ms) in males at 4h. For 100mg mirabegron, it was 7.70ms (9.72ms) in females and 4.63ms (6.45ms) in males at 4h, whereas for 200mg mirabegron it was 10.42ms (13.44ms) in females at 5h and 7.33ms (9.42ms) in males at 4h. Therefore as seen in other studies, QT prolongation was at the higher doses of 100 and 200mg was seen in this study.

Post-marketing pharmacovigilance data review:

Case 1: concerns an 80 year-old male patient who experienced edema of both legs aggravated and marked prolonged QT following 50 mg mirabegron treatment for overactive bladder. According to the reporting physician, regarding the adverse event QTc time prolonged: there was no previous occurrence, but the patient had hypertension, valvular disease of heart (mitral regurgitation, aortic regurgitation), hepatic disease, arrhythmia and other illnesses which could have been a trigger at present. There were no possibilities of congenital QT syndrome (prolonged or shortening), cardiac failure, congenital heart disease, or electrolyte abnormality or thyroid diseases. 06-Jul-2015: The patient had sinus bradycardia 56bpm + Ventricular Premature Contractions. and QT/QTc = 438/425 ms. The patient had trouble due to nocturia and so was started on mirabegron (oral, 50 mg/day) for overactive bladder. On 07-Aug-2015: Oedema of the lower limb was noted. S sodium (Na) = 144.2 and potassium (K) = 3.67. Trichlormethiazide 2 mg daily was initiated but worsening of oedema of both legs developed. 10-Sep-2015 Oedema of the lower limb decreased but increased again soon after. 30-Oct-2015. He had marked oedema in legs and a QTc of 454ms, that day, oedema in both feet advanced after the administration of mirabegron. Treatment with mirabegron was discontinued on the 30th October. By the 20-Nov2015: Oedema in both feet has completely disappeared and QT prolongation was reported as resolving. According to the physician oedema of both legs became particularly prominent while there were no remarkable changes in the state of/ the daily life of this patient, although there were backgrounds as listed in the reporting documents. Among the drugs on treatment, mirabegron was noted particular in this case. Knowing that there were reports regarding the effect of mirabegron on QTc prolongation, and checking the condition of edema after discontinuing (30-Oct-2015) only mirabegron at first, it was confirmed that the edema had completely subsided on 20-Nov-2015 when the patient visited the outpatient department for the first time after discontinuing the administration. Improvements in QT/QTc were also apparent, and thus the edema and QT prolongation was considered to be due to mirabegron. - JP-ASTELLAS-2015JP023961

Reviewer comment: *There is a temporal association between drug and events and a positive dechallenge. When the events happened, mirabegron was the only newly added drug. The patient had multiple cardiac conditions prior to administration with mirabegron however this case supports the idea that mirabegron may worsen existing heart disease through oedema and QT prolongation. Lower limb oedema is not an expected event for mirabegron. When assessed using the French causality assessment tool, the outcome is Uncertain. Time to onset was 4 weeks*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 2: Case concerning 31-year-old female patient who experienced disturbed consciousness, pneumonia aspiration, Torsade de Pointes, and QT prolongation following Betanis tablet (mirabegron) and Vesicare tablet (solifenacin) overdose. Other suspect drugs used were Risperdal (risperidone), Zosyn (piperacillin sodium, tazobactam sodium), and norepinephrine. Underlying diseases included schizophrenia, depression, and overactive bladder. Concomitant medications included flunitrazepam, lansoprazole, nitrazepam, etizolam, betamethasone, chlorphenamine maleate, milnacipran hydrochloride, and metoclopramide. Feb-2015: The patient took an over dose of mirabegron and solifenacin. 19-Feb-2015: patient was admitted to the reporting hospital unconscious. Activated charcoal and laxative were administered. The patient was kept under observation with transfusion therapy. Treatment with risperidone was discontinued. 20-Feb-2015: Disturbed consciousness remained, and aspiration pneumonia developed. piperacillin sodium, tazobactam sodium (vein, 1.5 g, thrice daily) and norepinephrine (vein, 0.3 mg/h, persistence) were used. QT prolongation, Torsade de Pointes, and ventricular tachycardia (VT) developed. 21-Feb-2015: Due to persistent disturbed consciousness noted in the morning, she was kept under observation for another night. In the evening,

there was a rapid decrease in blood pressure and QT prolongation occured at 464ms, with wide QRS tachycardia, as well as occasional Torsade de Pointes-like waves. From the mid night on 21-Feb-2015 through 22-Feb-2015, magnesium sulfate was administered and cardioversion was performed at 200J, which resulted in sinus rhythm. The treatment with noradrenaline was discontinued. 23-Feb-2015: Consciousness improved. In addition, significant improvement was seen in electrocardiogram changes. Electrocardiogram QT interval was 347 ms. The outcomes of disturbed consciousness, pneumonia aspiration, Torsade de Pointes, and QT prolongation were reported as resolving. The treatment with piperacillin sodium, tazobactam sodium was discontinued because pneumonia aspiration was resolving and the drug was switched to oral administration of Augmentin. 22-Apr-2015: The treatment with mirabegron (oral, 50 mg, once daily) and solifenacin (oral, 5 mg, once daily) was started again. Relapse of disturbed consciousness, pneumonia aspiration, Torsade de Pointes, and QT prolongation was not noted JP-ASTELLAS-2015JP023221

Reviewer comment: *There is a temporal association between drug and events and a positive dechallenge. It was not mentioned whether the prolonged QT interval was corrected for heart rate. According to mirabegron SPC, an interaction between solifenacin and mirabegron should not occur. Rechallenge with mirabegron at therapeutic doses did not cause a repeat effect. Post marketing cases of QT prolongation and arrhythmia were observed for solifenacin according to the Vesicare SmPC. At the time of the overdose the patient was also on risperidone which can also cause QT prolongation. Causality of mirabegron to QT prolongation was as assessed as Uncertain using the French method. Time to onset 1 day*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R-	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: case reported by a physician referring to an 85-year-old female patient who experienced ventricular tachycardia, QRS widened, immobility, and QTc prolonged following Betanis tablet 50 mg (mirabegron) treatment. No other suspect medications were reported. Underlying disease included overactive bladder, and neurogenic bladder; current condition included hypertension, spinal column stenosis, dementia, insomnia and dyslipidaemia; historical condition included brain contusion. Concomitant medications included urapidil, zolpidem tartrate, telmisartan, lansoprazole, donepezil hydrochloride, fudosteine, benidipine hydrochloride, pravastatin sodium, limaprost alfadex, mecobalamin, cyanocobalamin/lidocaine hydrochloride/pyridoxine hydrochloride/thiamine hydrochloride, diphenhydramine, and diclofenac sodium. Place of occurrence: Inside the residence. No similar symptoms were observed in the past, no congenital QT syndrome, no ischemic heart disease, no heart failure, no cardiac valvular disease, no congenital heart disease, no other heart disease, no electrolyte abnormality, no thyroid disease, no history of renal disease, no history of hepatic disease, no arrhythmia, no possibility of drug interaction, no disease or abnormality to trigger, no ablation operation, no family history of congenital QT syndrome or cardiovascular disease. Mirabegron (oral, 50 mg, once daily) was started for overactive bladder. 14-Nov-2015: The patient lived with her eldest son. Her son was not at home in daytime due to job. Her son took her oral medications for a day from their package, separated them for morning, noon, and evening, and put them in a pill case. When he returned to the home around 8 p.m., shutters were not closed, and a light at toilet was turned on. He moved to the bed of the patient, and found that the patient was saying "I cannot move" under her bed. Immobility developed. He checked the oral medications, and those for morning and noon were not in the case, but those for evening were left. Also, empty packages of mirabegron (those were not put in the pill case) were scattered around, so he called an ambulance (overdose). There were no other empty packages. The empty packages were for 39 tablets of mirabegron. At 10:59 p.m., when an ambulance arrived, her level of consciousness (JCS) was 3, breathing 23/minute, pulse 48/minute, blood pressure 105/78, body temperature 34.3 degrees Celsius, oxygen saturation (SpO2) 99%. At 11:28 p.m., when the ambulance arrived at the hospital, E3V4M6,

pulse 130/minute, blood pressure 130/69, SpO2: Peripheral coldness was significant, immeasurable. 12-lead (electrocardiogram), ECG: Wide width QRS, wave like ventricular tachycardia (VT). The electrocardiogram revealed significant QT prolonged and QRS widened. QTc and QRS wides were immeasurable. It was considered that this was likely an abnormal electrocardiogram due to mirabegron overdose. The patient had dementia. Details of administration prehistory were unknown. The patient was hospitalized in intensive care unit (ICU). There she lost consciousness and developed tachycardia. Nov-2015: Treatment with mirabegron was discontinued (not readministered). 15-Nov-2015: Mirabegron level in blood (serum) was 1820 ng/mL. A and V sheaths were prepared to introduce V-A extracorporeal membrane oxygenation (ECMO) as a measure against ventricular fibrillation. Mirabegron level in blood (plasma) in a blood collection just before direct hemoperfusion (DHP) was 739 ng/mL. A CV catheter was inserted into the right internal carotid artery for the purpose of DHP and continuous hemodiafiltration (CHDF). Direct hemoperfusion using activated charcoal was performed. The first session of DHP was performed for two hours (1:15 a.m. to 3:15 a.m.); then shifted to CHDF at 2 a.m. At 6 a.m., the waves changed to QRS 216 ms and QTc 543 ms. The patient was improved to measurable level. At 10 a.m., intravenous bolus of 20% fat preparation (Intralipos) 100 mL was given and thereafter continued at 0.5 mL/kg/h. At 12 p.m., intravenous Intralipos 50 mL was administered. After intravenous administration of Intralipos in total 250 mL, QTc improved to 481 ms and QRS wide to 160 ms. Administration was completed. The second session of DHP was performed for two hours (3 p.m. to 5 p.m). QTc and QRS wide only slightly improved. CHDF was not resumed and the procedure was completed at 5 p.m. Mirabegron level in blood (serum) in a blood collection after DHP was 519 ng/mL. Afterward, QTc and QRS wide were improving. Information about poisoning symptoms and treatment was provided by Japan Poison Information center on the same day. 16-Nov-2015: Mirabegron level in blood (serum) was 137 ng/mL. Mirabegron level in blood (serum) was 105 ng/mL. 17-Nov-2015 (4th day of illness): The bedside monitor showed ECG waveform being normalized at 12:20 am. QTc was normalized by the morning. JP-ASTELLAS-2015JP022850

Reviewer comment: *There is a close temporal association between drug and the QT interval prolongation occurring in the ambulance, just hours after administration of the overdose. There is also a positive dechallenge. Mirabegron was the only drug used in overdose. Causality was assessed as highly probable in this case. Furthermore, Intralipos (bolus fat solution) administration together with haemoperfusion appear to be effective in the treatment of mirabegron overdose induced QT prolongation. Time to onset 0 days*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L+
Dechallenge	C3	Alternate	S3
Result	I4	Highly probable	

Case 4: concerns a 62 years-old male patient who experienced palpitations, tachycardia, QT prolonged, hypomagnesaemia, drug interaction with TS-1 (tegafur/gimeracil/oteracil potassium), diarrhoea, and constipation following Betanis tablet 50 mg (mirabegron) treatment for overactive bladder. Concurrent medical conditions include squamous cell carcinoma of the lung, idiopathic interstitial pneumonia, type 2 diabetes mellitus, hypertension, post-abdominal aortic aneurysm surgery, exercise lack of, and electrolyte abnormality; allergy to alcohol and none smoker; historical condition included abdominal aortic aneurysm and acute arterial occlusion of the lower extremity. Patient was on carbocisteine, montelukast sodium, glimepiride, metformin hydrochloride, alogliptin benzoate/pioglitazone hydrochloride, and olmesartan medoxomil. 17-Nov-2015: The patients QTc was 448ms with complete right bundle branch block. 09-Jan-2016: The patient started to receive tegafur/gimeracil/oteracil potassium (oral, 60 mg, twice daily) for squamous cell carcinoma of lung. 22-Jan-2016: TS-1 was discontinued. On 29-Jan-2016 the patient experienced nocturia and the condition was diagnosed as overactive bladder in consultation with an urologist. The patient started to

receive mirabegron (oral, 50 mg, once daily). 18-Feb-2016: Chemotherapy was performed. As constipation which seemed to be affected by chemotherapy developed, magnesium oxide (oral, 660 mg, thrice daily) was initiated. The patient became aware of palpitations and exercise-induced shortness of breath. Palpitations developed. The pulse increased to approximately 120/minute. 20-Feb-2016: Diarrhoea developed. Treatment with magnesium oxide was discontinued. 02-Mar-2016: At 08:54:27, Pulse was around 110/minute, QTc was 482ms, and palpitations were noted. Tachycardia and more QT prolonged developed with clinical manifestations and symptoms present: palpitations, arrhythmia, shortness of breath, tachycardia). The blood magnesium level was 1.2 (range 1.3-2.1 mEq/L). Hypomagnesaemia was confirmed at blood collection. As it was mild, treatment was not provided and the patient was followed up. Adverse reaction of mirabegron was suspected, and mirabegron was discontinued (readministration: not provided). After discontinuation of mirabegron, pulse improved to around 90/minute. Palpitations improved while exercise-induced shortness of breath lingered. 10-Mar-2016: Pulse improved to around 70/minute, which was at the same level as the previous pulse. 23-Mar-2016: Pulse was around 90/minute, which was higher than the previous level; however, palpitations disappeared and exercise-induced shortness of breath slightly improved. The outcome of palpitations was reported as resolved. The outcomes of QT prolonged, tachycardia, and drug interaction with TS-1 were reported as resolving The outcome of hypomagnesaemia was reported as not resolved (treatment of hypomagnesaemia: not provided). The blood magnesium level was 1.2 mg/dL. 13-Apr-2016: The symptoms of tachycardia and palpitations had disappeared, but electrocardiography was not performed again. The physician assessed the following events with respect to mirabegron:-Palpitations (causality: Possible; causative factor other than mirabegron: None). Tachycardia (causality: Possible; causative factor other than mirabegron: TS-1 and hypomagnesaemia)- QT prolonged (seriousness: Medically Significant; causality: Possible; causative factor other than mirabegron: TS-1 and hypomagnesaemia) JP-ASTELLAS-2016JP004250AA

Reviewer comment: *There is a temporal association between drug and events and a positive dechallenge. Time to onset was 20 days. This case was initially confounded by the administration of magnesium in very high dose which could have been seen to contribute to the palpitations and exercise-induced shortness of breath however these events persisted, even when magnesium levels were at normal levels. This case lends support to a contribution of mirabegron to QT prolongation. Outcome according to the French tool of causality assessment is Possible.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 5: Referring to a male patient who experienced prolonged QT intervals on ECG during Betmiga (mirabegron) treatment. No other suspect medications were reported. The patient received mirabegron for a few months. GB-ASTELLAS-2016US025948

Reviewer comment: *Temporality is compatable in this case. There is very little information to assess this case. Outcome using French tool is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 6: 81-year-old female experienced QT prolonged during Betanis (mirabegron) treatment. Medical history included: overactive bladder as an underlying disease, suspected ovarian tumor as a current condition and breast cancer as a historical condition. She was on no concomitant drugs. On 14MAR2013, the patient started mirabegron oral 50 mg daily for overactive bladder. On 01APR2013, QT prolonged developed at 490ms, chest pain, palpitations and shortness of breath. Mirabegron treatment was discontinued on the same date. The patient received no symptomatic treatment and the outcome of the event was unknown. The reporting physician considered there were no causative factors other than mirabegron as there were no other risk factors and no other past similar episodes, congenital QT syndrome (long or short),ischemic heart disease, heart failure, hypertension, diabetes, electrolyte abnormalities, thyroid disease, history of renal impairment or renal disease and history of hepatic impairment. JP-ASTELLAS-2013JP010094

Reviewer comment: *A temporal relationship exists. Time to onset of 15 days very little other information.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 7: concerns a 90 year old female who developed increase in QT interval with Myrbetriq(mirabegron) therapy. On 30SEP2013, she began mirabegron, 50 mg daily for incontinence. She had great results with mirabegron and reported zero incontinence shortly after starting mirabegron. On 15NOV2013, her nurse practitioner detected an increase in her QT interval. Approximately a week later, mirabegron therapy was discontinued. Outcome of QT prolongation is resolved -US-ASTELLAS-2013US012595

Reviewer comment: *Temporal relationship exists, very little information is given in this case. Time to onset/detection was 6 weeks. Causality assessed as possible.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 8: involves a female patient of unknown age who reported QT prolonged after starting fexofenadine hydrochloride (Allegra). On an unknown date, she also started therapy with mirabegron via oral route (dose and frequency unknown). On an unknown date, electrocardiogram test showed QT prolonged. The event was unlikely to be associated with fexofenadine hydrochloride according to the dermatologist's comment. JP-SA-2014SA056830

Reviewer comment: *Temporal relationship, no alternate explanation. Fexofenadine at suprathereutic doses was not seen to prolong the QT interval in through QT study with fexofenadine (as per SmPC). Causality assessed as Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 9: referring to a 76 year-old male patient who experienced QT interval prolonged during Betanis tablet 50 mg (mirabegron) treatment. No other suspect medications were reported. Underlying disease included overactive bladder; current conditions included ventricular extrasystoles, hypertension, and prostatic hyperplasia; historical condition included myocardial infarction, procedure included percutaneous transluminal coronary angioplasty (PTCA), and non-tobacco user. Concomitant medication included serenoa repens (saw palmetto). On 14-Dec-2013: The patient received mirabegron (oral 50 mg, once daily) for overactive bladder at 8:00am. At 9.16am the QTcF was 437ms/At 9.18 the QTcF was 463ms/At 9.20 the QTcF was 458ms . On 04-Jun-2014: The outcome of QT interval prolonged was unknown and mirabegron treatment was ongoing.[Physicians Comment] QT interval prolonged was considered as incidental. JP-ASTELLAS-2014JP003290

Reviewer comment: *Temporal relationship, no alternate explanation. Reaction happened 1 hr twenty minutes after drug administration but it was not reported whether it persisted or not in the hours later. Since mirabegron treatment was maintained it is possible that QT interval normalized. Causality assessment judged as Possible using the French method.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S3
Result	I2	Possible	

Case 10: case referring to a patient who experienced QT prolongation during Myrbetriq (mirabegron) treatment GB-ASTELLAS-2014US019041
Reviewer comment: *Not assessable*

Case 11: 52 years-old female patient experienced QT prolonged following Betanis (mirabegron) treatment. No other suspect medications were reported. Underlying diseases included overactive bladder; and current condition included arrhythmia. Concomitant medication included tolterodine tartrate. The patient was previously on detrusitol but was switched to Betanis (oral, 50 mg, once daily). On 12-Feb-2013: before mirabegron administration (11:30:25) QT/QTcF was 357/415ms (oral, 50 mg, once daily) and mirabegron was initiated for overactive bladder. On 10-Apr-2014: The patient visited the hospital as Betanis ran out. The patient was checked for QT prolonged and at 11:25am QT/QTcF was: 399/460ms, (11:26:14) QT/QTcF: 403/464ms, (11:27:35). Mirabegron treatment was ongoing. The pharmaceutical company reviewers assessed QT prolonged as serious due to medical significance and the causal relationship to Mirabegron as possible. Using the French tool outcome is also Possible. JP-ASTELLAS-2013JP009361

Reviewer comment: *Temporal relationship, no alternate explanation. Time to onset/detection was 8 weeks. Causality assessment using French tool outcomes Possible.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S3
Result	I2	Possible	

Case 12: case referring to a 66-year-old male patient who experienced ventricular extrasystoles and prolonged QT interval following Betanis tablet 25 mg (mirabegron) treatment. No other suspect medications were reported. Underlying disease included overactive bladder; current conditions included incomplete right bundle branch block, hypertension, gout, cerebral infarction (right sided hemiplegia), and prostatic hyperplasia; historical condition included angina pectoris; historical drug reactions included drug eruptions. and chest pain; past procedures included coronary artery bypass graft (CABG). Concomitant medications included nifedipine, candesartan cilexetil, aspirin, cilostazol, diclofenac sodium, dutasteride, tamsulosin, and serenoa repens (saw palmetto). On 27MAY2013, the patient started mirabegron (oral 25 mg, once daily) for overactive bladder. Electrocardiogram (ECG) of the patient was performed and showed abnormalities (incomplete right bundle branch block and first-degree atrioventricular block). QT values were as follows: 431 ms (12:09:13), 436 ms (12:10:02), and 437 ms (12:10:49). On 24JUN2013 (Week 4), the patient took mirabegron before electrocardiography. ECG was performed and showed abnormalities (unsuitable for QT analysis, ventricular extrasystoles, incomplete right bundle branch block, prolonged QT interval, and multiple ventricular extrasystoles with right bundle branch block and inferior axis in the trigeminy). Mirabegron treatment was discontinued due to ineffectiveness. On 29JUL2013, ECG showed abnormalities. The patient's QT values were as follows: 437 ms (11:01:30), 435 ms (11:02:16), and 440 ms (11:03:02). The patient did not take mirabegron. ECG (after the discontinuation of mirabegron treatment) showed that ventricular extrasystoles observed at week 4 disappeared and returned to the condition before mirabegron treatment. The outcome of ventricular extrasystoles was recovering (Treatment for ventricular extrasystoles: Absent). On an unspecified date, the outcome of prolonged QT interval was not reported. Mirabegron was not readministered. The ventricular extrasystoles developed after taking mirabegron and disappeared after the discontinuation of mirabegron treatment, and thus the causal relationship of the event to mirabegron could not be completely ruled out. On the other hand, the patient had a history of coronary artery bypass surgery in 2000. In this investigation, in consideration of daily fluctuations of electrocardiographic complex, electrical conduction system of the heart was in an unstable condition. Thus, the possibility of the event attributable to mirabegron was low. Prolonged QT interval (QTcF above 450 msec) and first degree atrioventricular block were observed on 29JUL2013 and 27MAY2013 respectively. These symptoms were considered to be part of the symptoms of the comorbid arrhythmia. The current conditions were causative factors for the ventricular extrasystoles other than Betanis. JP-ASTELLAS-2013JP010103

Reviewer comment: *It is unclear whether QT interval prolongation was present before the start of treatment with mirbaegron or not as from the report it would appear the first ECG was taken on the day of start of treatment. Discontinuation of mirabegron did not resolve QT interval prolongation however for the ventricular extrasystoles, these developed after taking mirabegron and disappeared after the discontinuation of mirabegron treatment. It seems that in this patient, a previous cardiac condition (possibly with QT prolongation already present) was slightly worsened on treatment with mirabegron. It did not reach clinical symptoms of arrhythmias or ventricular tachycardia however.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 13: refers to an 89-year-old male patient on Ranmark (denosumab)and Betanis (mirabegron). The patient's medical history included prostate cancer, metastases to bone, cardiac hypertrophy, and abdominal aortic aneurysm. Concomitant medications reported included zoladex (goserelin acetate), Norvasc (amlodipine besilate), Bayaspirin (acetylsalicylic acid), arotinolol, Crestor (rosuvastatin calcium), and Baycaron (mefruside).On an unknown date, electrocardiogram (ECG) examination revealed QT prolongation. Laboratory investigation performed from 05/Aug/2014 to 12/Mar/2015 revealed: blood albumin 3.8 to 4.3 g/dL and blood calcium 8.4 to 9.3 mg/dL (both in range). No treatment information was provided. The outcome of the event of QT prolonged was reported as resolved on 20/Aug/2014. The pharmacist considered the event of QT prolonged was not related to Ranmark (denosumab). Betanis was considered as co-suspect medication. JP-DSJP-DSJ-2015-104583

Reviewer comment: *Temporal relationship, no alternative explanation give in this case. Denosumab is not expected to cause QT prolongation according to the Prolia SmPC. French method causality assessment outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 14: a case from a Japanese interventional post authorization study reported by a physician, referring to a 74-year-old female patient who experienced giant negative T wave, aggravation of prolonged QT, coronary arteriography, vulvitis, dry mouth, and constipation following Betanis tablets 50 mg (mirabegron) treatment. The patient, S05006, was enrolled in open label study 178-CL-112: Long-term Add on Therapy with Anticholinergics under Treatment with Mirabegron. Other suspect drug used was BUP-4 (propiverine hydrochloride). Underlying disease included overactive bladder; and current condition included hyperlipidaemia, diabetes mellitus, insomnia, binocular conjunctivitis, complete right bundle branch block, PR prolongation, and prolonged QT. Concomitant medications included pravastatin sodium, miglitol, glimepiride, vildagliptin, metformin hydrochloride, brotizolam, cyanocobalamin, levocabastine hydrochloride, and betamethasone valerate, gentamicin sulfate cream, diazepam, insulin glargine, liraglutide, and acetylsalicylic acid. 02-Oct-2014: The patient started to receive mirabegron (oral 50 mg daily) for overactive bladder (pretreatment). 10-Dec-2014: Mirabegron treatment was completed. The patient was temporarily registered (observation period started). The result of electrocardiographic measurement at 2W was "Abnormal ECG, possibly significant". After consideration it was decided to include the patient in the study. QTcF at this point was 455, 450, 465.
11-Dec-2014: Treatment was switched to mirabegron study drug (oral 50 mg once daily after breakfast) for overactive bladder. 12-Dec-2014: According to the electrocardiographic analysis, despite the complete right bundle branch block, mild PR prolongation and prolonged QT, an advisor on electrocardiography decided that there was no problem to include the patient in the study. 24-Dec-2014: The patient was officially registered. 25-Dec-2014: The patient started to receive propiverine hydrochloride (oral 20 mg once daily after breakfast) for overactive bladder. 26-Jan-2015: The patient made a week 4 visit. On electrocardiographic measurement during 4W, although the results of 3 times of measurements were all "Abnormal ECG, possibly significant", in comparison of during 2W (10-Dec-2014), the result was "No clinically significant change", and it was considered that there was no problem in continuation. 14-Feb-2015: The patient felt itch on vulva. The patient developed vulvitis. 17-Feb-2015: The patient made a week 8 visit (Visit 4). The patient was complaining of vulvar pruritus since 3 days before visiting the hospital. The seriousness of vulvitis was judged to be mild. The patient started to receive betamethasone valerate, gentamicin sulfate cream (topical, adequate dose) as a treatment for vulvitis. On electrocardiographic measurement during 8W, although the results of 3 times of measurements were all "Abnormal ECG possibly significant", in comparison of during 2W (10-Dec-2014), the result was "No clinically significant change", and it was considered that there was no problem in continuation. 18-Feb-2015: As criterion for anticholinergic drug dose increase was met

and there was no problem in safety, the dose of propiverine hydrochloride was increased to 20 mg twice daily after breakfast and dinner for overactive bladder. 19-Feb-2015: The patient complained of dry mouth with throat itches. Dry mouth developed. No particular treatment was provided. Constipation developed. The patient complained of hard stool resulting in the excretion frequency changed from once/day to once/2day, following dose increase of anticholinergic drug (propiverine hydrochloride). No particular treatment was provided. 23-Feb-2015: The treatment with betamethasone valerate, gentamicin sulfate cream, was completed. 24-Feb-2015: The outcome of vulvitis was reported as recovered/resolved. 17-Mar-2015: The patient made a week 12 visit (Visit 5). On electrocardiographic measurement during 12W, although the results of 3 time of measurements were all "Abnormal ECG, possibly significant", in comparison of during 2W (10-Dec-2014), the result was "No clinically significant change", and it was decided that there was no problem in continuation of the study, same as at week 4. (Dec-2014). 08-Apr-2015: Giant negative T wave and aggravation of prolonged QT developed. The severity was mild. The patient made a week 16 visit. On electrocardiographic measurement during 16W, although the results of 3 times of measurements were all "Abnormal ECG, possibly significant", in comparison of during 2W (10-Dec-2014), the result was "Clinical correlation needed for changes". The patient was planned for educational hospitalization for diabetes mellitus at another hospital. QTcF: 491, 494, 495. Results of electrocardiography performed on 08-Apr showed giant negative T wave and dominant prolonged QT in wide induction, in addition to the complete right bundle branch block and left axis deviation. The electrocardiographic advisor decided that the causal relationship of the study drug with the events could not be ruled out and that the study should be discontinued. 15-Apr-2015: Based on the advisor's decision, the study was discontinued for the clinically significant abnormal conditions. Examinations on discontinuation were performed. 16-Apr-2015: As no patient's jeopardy was considered, the drug was switched to mirabegron oral 50 mg daily and it was administrated continuously for overactive bladder as usual treatment. 18-Apr-2015: According to the judgment result of electrocardiographic adviser, the finding of giant negative T wave and aggravation of prolonged QT was the same as the time of 16W. 20-Apr-2015: the patient was admitted to the other hospital for diabetes mellitus education. 08-May-2015: The patient visited the hospital as an outpatient. Dry mouth and constipation had regressed. The outcome of dry mouth and constipation was resolved. The patient had been advised to visit the department of cardiovascular medicine since the discontinuation of the study, but had not yet visited there. As she had no symptoms and the results of examination on discontinuation did not show any exacerbation compared to those of 16W. 04-Jun-2015: It was reported that the patient underwent thorough examinations as a result of electrocardiography performed at the other hospital, and CT results showed that one of the cardiac blood vessels coarctated which required surgery. 23-Jun-2015: The patient was admitted to the other hospital for an examination (coronary arteriography) of suspected ischemic heart disease. Jun-2015: Coronary arteriography was performed. No significant stenosis was observed. Lactec injection 1500 ml daily, Omnipaque 34 ml daily, and Xylocaine Polyamp 10 ml daily were used for coronary arteriography. 27-Jun-2015: The patient was discharged from the other hospital without any intervention or treatment. The outcome of coronary arteriography was reported as resolved. 22-Jul-2015: The patient visited the reporting hospital. Follow-up electrocardiography was performed. The results of electrocardiography showed the following QTcF: 469, 467, and 473. In addition, the drugs being taken by the patient were confirmed by the patient's report and her medication notebook. The outcome of giant negative T wave and aggravation of prolonged QT was reported as not resolved. 24-Jul-2015: The results of electrocardiography performed on 22-Jul-2015 were obtained, and it was confirmed that there had been no significant changes since the week 16 visit. Patient referral document received on 22-Jul-2015 from the other hospital was also confirmed. It revealed that no significant stenosis was observed as a result of coronary arteriography and that no intervention or treatment was performed. The purpose of the hospitalization was not a surgery but an examination for suspected ischemic heart disease, and the suspected symptom was ruled out. As a result of reconsideration based on the information provided from the other hospital, it was determined to report the hospitalization for suspected ischemic heart disease (from 23-Jun-2015 to 27-Jun-2015) as a different event, coronary arteriography, and the event was considered as resolved as of 27-Jun, when the patient was discharged. It was decided to continue the follow-up of giant negative T wave, an electrocardiographic abnormality. The assessments on giant negative T wave and aggravation of prolonged QT regarding its outcome, etc. were scheduled to be conducted when an evaluation report of electrocardiography was received. Mirabegron treatment was ongoing. [Physician comment obtained from the monitor]- Giant negative T wave: Since the event developed during mirabegron

study drug and propiverine hydrochloride study drug treatment, the causality with both medicines cannot be denied. The study drug's action mechanism, treatment period, and the results of electrocardiography indicated the possibility of study drug's involvement in the event. JP-ASTELLAS-2015JP004550

Reviewer comment: *Temporal relationship with the administration of both mirabegron and propiverine hydrochloride. QT prolongation is not an expected ADR for propiverine. It would appear from this case that these two drugs could have contributed to the worsening of this patients QT interval from readings of 455, 450, 465 to readings of 491, 494, 495. This patient was not clinically symptomatic however and had no palipiations or arrhythmias. Using the French tool, the outcome in this case is Probable.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R+	Lab Test	L0
Dechallenge	C3	Alternate	S1
Result	I3	Probable	

Case 15: 19-Aug-2015. physician reports of a male patient who experienced increase in QTC prolongation during Myrbetriq (mirabegron) treatment. No other suspect medications were reported. Current condition included cardiovascular (CV) concerns. On an unspecified date, the patient developed an increase in QTC prolongation. It was reported that once mirabegron treatment was taken off, the patient was fine. The patient was on Vesicare (solifenacin) at the time of report and was no longer experiencing any QTc prolongation. CA-ASTELLAS-2015US029938

Reviewer comment: *Temporal relationship and positive dechallenge make the causality assessment Possible. An alternative explanation is his cardiac concerns.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S1
Result	I2	Possible	

Overall signal assessment using Bradford-Hill (BH) criteria:

Active substance	BH criterium	Assessment
MIRABEGRON	Strength of association	1.22 PRR, 14 ADR Case reports 8 of which causality possible probable or highly probable, 7 articles directly relevant to QT effects were retrieved from the literature.
	Biological Plausibility	Mirabegron prolonged the QT interval and blocked the hERG (human ether-a-go-go-related gene) channel current in *in vitro* laboratory models. QTc prolongation was seen in the clinical setting in human studies. Mirabegron had an Ikr inhibition of 14.7% at 30 µmol/L. Mirabegron metabolites M5 and M16 inhibited hERG current, with respective IC50 values of 21 and 31 µmol/L, and 17.3% for M14 although these effects were seen at concentrations considerably higher than the expected Cmax in humans. The observed effects of mirabegron on cardiac muscle action potential were not significant, but its M5 metabolite at 3 µmol/L prolonged slightly APD30 by 6.1% and shortened APD30-90 by 7.9%, while concentrations of 30 µmol/L prolonged APD30 by 5.6% and APD90 by 4.7%. M16 prolonged APD90 by 5.0% at 30 µmol/L.
	Biological gradient	Increased QT interval prolongation was seen with increasing doses of mirabegron.
	Experimental evidence and temporality	Of the 14 cases assessed, all had a temporal relationship between the events and the initiation of treatment. Some cases were confounded by other drugs and some occurred in the presence of underlying cardiac conditions. It would appear that this patient group is the most susceptible to adverse events for treatment with mirabegron. In 6/14 cases mirabegron was the only suspect drug and in 4 cases decreases in the dosage or stopping treatment with mirabegron resolved the symptoms (positive dechallenge).
	Consistency	2 cases had the same profiles, ie. QT prolongation plus ventricular premature contractions and ventricular extrasystoles. Reports originate from different countries, in EU and non EU with possibly different prescribing patters and levels of use. The signal involves both healthy volunteers (experimental evidence) and postmarketing evidence.
	Specificity	In preclinical data mirabegron and its metabolites was found to bind and block the hERG potassium channel and prolong

		the action potential.
	Analogy	Mirabegron is the only product for OAB authorised in EU which is a selective agonist for human beta 3-adrenoceptor (beta 3-AR).
Overall assessment	*In the Eudravigilance database the association of mirabegron with QT prolongation was disproportionally reported for this drug over others. Literature and case review supports the relation, and preclinical data demonstrates a mechanism of action. The current SmPC for mirabegron insufficiently informs on the risk of QT interval prolongation with this drug. Action is warranted to change SmPC sections 4.4 and 4.8 on the basis of literature review and case assessment as well as biological plausibility demonstrated by pre clinical data. Furthermore, clinicians should be informed of these SmPC changes through a DHPC of the following recommendations;* *1. To evaluate patients prior to treatment with mirabegron for risk factors for QT prolongation and if several risk factors are present to use other urologicals with less potential to cause QT prolongation such as the anticholinergic agents oxybutynin and tolterodine.* *2. If no alternative can be used, monitoring is recommended. Consider obtaining an ECG and serum potassium levels following initiation of the drug.* *3. Additional ECG monitoring should be considered with any dose increase or the addition of other drugs which also carry QT prolongation risk*	
Benefit Risk Balance	*The benefit risk balance of this product remains positive.*	

Appendix 4:
Pantoprazole

Malta, January2017

Signal Description Message

From	To	Copy to
Amy Tanti	Post-Licensing Directorate	Professor John J Borg

Subject

Medicinal product	Pantoprazole20mg gastro-resistant tablets
Signal (MedDRA term)	Electrocardiogram QT interval prolonged (investigated) Hypokalaemia (detected)

Priority Grade Proposal:

Important risk

Summary

Imputability Score	**Number of case**
I4-Highly Probable	0
I3-Probable	1
I2-Possible	2
I1-Uncertain	15
I0 -Unlikely	1

Signal characteristics

Source (database, literature…)	Eudravigilance database, medical literature, company clinical and pre-clinical data
Number of reports	21 total, 19 assessable 9 EU, 12 Non-EU
Expectedness	No
Seriousness	Yes Drug induced QT interval prolongation predisposes to arrhythmias, including the lethal Torsade de Pointes.
Statistics (if available, e.g. PRR, IC, confidence interval…)	

Reaction PT	PRR (-)	PRR	PRR (+)	Static PRR Analysis - CHI^2
Electrocardiogram QT prolonged	0.691030545	1.0076424	1.46931742	0.001565127

Pantoprazole: Pantoloc Control® 20mg gastro-resistant tablets

Mechanism of action: Pantroprazole inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole is converted to its active form, a cyclic sulphenamide, in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach.

Date EU approval: 12th June 2009

Indication: for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

Availability in MT: available

Currently authorised SmPC wording:

Section	Wording
4.3 Contraindications	Not listed
4.4 Warnings	Not listed
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

Company preclinical and clinical data

The dossier available for this centralised procedure was for a generic medicinal product with a nationally authorised reference product. This means that the full set of tests done in the preclinical setting with the originator product where not available within the package available for this study. Regarding clinical data the company stated the following in their submission data;

Regarding clinical data, the company described an in-depth safety analysis of cardiovascular events within report 364/2007 which revealed no signal of an association of coronary artery disorders with pantoprazole use. Upon the request of the FDA (referring to the potential for cardiovascular risk related to the use of omeprazole and esomeprazole) information on cardiovascular AEs associated with pantoprazole was provided. The FDA subsequently stated that there is no evidence that PPIs increase the risk for cardiovascular events

Scientific literature

When the literature was searched for pantoprazole and QT interval prolongation a number of case report literature was retrieved but since the same cases were reported in the Eudravigilance database, the published reports are dealt with in that section.
During the course of scientific evaluation of the signal between QT prolongation and pantoprazole an emerging issue became apparent. From the cases assessed, the use of pantoprazole coincided with electrolyte disturbances namely hypomagnesaemia and hypokalaemia. In some literature review, the authors discuss a possible mechanism of hypomagneaesmia induced kaliuresis as well as interferences with potassium ionic excghange in the parietal cells of the gastric wall resulting in potassium loss via the gastric pathway.
A major risk factor for QT interval prolongation is hypokaleamia. While hypomagneasemia is a labelled event within the product information of pantoprazole and other proton pump inhibitors (PPIs), hypokalemia is not a labelled effect for pantoprazole or the other PPIs.
The association between pantoprazole and QT interval prolongation may therefore be an indirect effect of hypermagnaesmia induced kaliuresis caused by pantoprazole, or hypokalaemia induced by gastric losses via interference with the H+/K+ ATPase pump as per its primary mode of action.
The literature review therefore, in the case of pantoprazole, has been widened to include studies on this matter. Of interest is that both the FDA and the Credible Meds website (a U.S. dedicated website on drug induced QT prolongation) Credible Meds have both acknowledged the risk of hypokalemia with pantoprazole.

Woosley et al (2014) Pantoprazole now on Conditional TdP Risk List [1]

After receiving a report of cardiac arrest in a patient who was taking long-term esomeprazole therapy, CredibleMeds® analyzed the available cardiac safety data for each of the six proton pump inhibitors (PPIs) marketed in the US for the treatment of gastro-esophageal reflux disease (GERD). All six PPIs have uniform product labeling that includes a warning of rare but serious episodes of hypomagnesemia (low serum magnesium) associated with prolonged therapy (>3-12 months) (See FDA warning March 2011). These warning are supported by numerous case reports in the medical literature and hundreds of reports submitted to the FDA's Adverse Event Reporting System (AERS).
Because the prolonged use of a PPI can cause hypomagnesemia and hypokalemia, conditions that prolong cardiac repolarization and facilitate torsades de pointes (TdP) cardiac arrhythmia, it is biologically plausible that chronic PPI therapy can result in TdP. After review of the available evidence, CredibleMeds® has concluded that, at this time, pantoprazole (Protonix® brand in the US)* should be added to the list of drugs with "Conditional Risk of TdP." For the other PPIs (omeprazole, esomeprazole, lansoprazole, dexlansoprazole and rabeprazole), there are case reports in the literature

Woosley, RL, Heise, CW and Romero [1] *www.CredibleMeds.org, QTdrugs List, [Accessed 22.01.2017], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755*

and numerous reports of QT prolongation, TdP and cardiac death in AERS but the evidence has not yet met the CredibleMeds® threshold for causality.
In summary, CredibleMeds® has added pantoprazole to the "Conditional TdP Risk" list because of substantial and convincing evidence that, when taken for extended periods of time, this drug can cause hypomagnesemia and/or hypokalemia and indirectly result in TdP. Pantoprazole has also been added to the list of "Drugs to Avoid in Patients with congenital Long QT. Prolonged use (>14 days) of any PPI should be discouraged in this special population because of their inherent high risk of TdP.

Luk et al (2013) Proton Pump Inhibitor–Associated Hypomagnesemia: What Do FDA Data Tell Us?

Objective: To address the association between the use of different PPIs and hypomagnesemia by examining the frequency of occurrence of hypomagnesemia among the reported adverse drug reactions from the Food and Drug Administration (FDA) Adverse Event Reporting System database. Methods: We conducted a cross-sectional study of PPI-associated adverse effect cases reported to the FDA between November 1, 1997, and April 1, 2012. Logistic regression was used to examine the association of sex, age, and different PPIs with hypomagnesemia. $\chi 2$ Analysis was conducted to investigate the association of PPIassociated hypomagnesemia with hypocalcemia and hypokalemia. results: Among 66,102 subjects identified as experiencing 1 or more adverse effects while taking a PPI, 1.0% (n = 693) were reported to have hypomagnesemia. The mean (SD) age of PPI users presenting with hypomagnesemia was 64.4 (12.9) years. Results from logistic regression indicated that, compared with esomeprazole, all other PPIs had a higher rate of hypomagnesemia, with pantoprazole having the highest rate (OR 4.3; 95% CI 3.3-5.7; $p < 0.001$). The risk of female subjects having hypomagnesemia (OR 0.83; 95% CI 0.71-0.97; $p = 0.016$) was significantly lower than that of males. Elderly subjects (age >65 years) were at increased risk of PPI associated hypomagnesemia (OR 1.5; 95% CI 1.2-1.7; $p < 0.001$). $\chi 2$ Analysis showed strong association between hypomagnesemia and both hypocalcemia ($p < 0.001$) and hypokalemia ($p < 0.001$). Conclusions: All PPIs were associated with hypomagnesemia, with esomeprazole having the lowest risk and pantoprazole having the highest risk. The risk of PPI-associated hypomagnesemia was higher in males and the elderly population. Hypocalcemia and hypokalemia commonly coexisted with PPI-associated hypomagnesemia. (Luk et al, 2013)

Negri et al (2013) Hypomagnesaemia/hypokalemia associated with the use of esomeprazole.

Magnesium homeostasis is essential for many intracellular processes and depends on dynamic interplay of intestinal absorption, exchange with the bone reservoir, and renal excretion. Hypomagnesaemia may arise from various disorders. We review the case of a 59 year-old man whose only complaint was irritability with a routine analysis showing hypomagnesaemia and hypokalemia while using esomeprazole, a proton pump inhibitor (PPI). Fractional magnesium excretion was low, excluding excessive renal loss. Potassium excretion was 80 mEq/24 Hr in the presence of hypokalemia suggesting hypomagnesaemia-induced kaliuresis as its cause. Hypomagnesaemia partially resolved after oral magnesium supplementation. Esomeprazol suppression corrected hypomagnesaemia. A causal relationship with esomeprazol use was supported by the recurrence of hypomagnesaemia after rechallenge. We review the literature on hypomagnesaemia due to the use of proton pump inhibitors. In the past decade our understanding of transcellular magnesium transport was enhanced by the discovery of the magnesium channel, transient receptor potential (TR PM) 6 and 7 and other proteins that play an important role in its transport. In this light we discuss the possible etiology of proton pump inhibitor related hypomagnesaemia/hypokalemia.

Jhaveri (2012) Detective Nephron: A case of Hypomagnesemia [2]

[2] ASN Kidney News | January 2012 accessed 22.01.2017 [Internet], available from http://www.kidneynews.org/kidneynews/4_1/18/18.pdf

Detective Nephron, world-renowned for expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. L. O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron (angry)	My assistant is late today.
L. O. Henle enters the room with excitement.	
Nephron	What do you want?
Henle	I…I have a case for us.
Nephron	You are late today.
Henle	Hypomagnesemia
Nephron (with surprise)	Excellent. A good case can change my mood.
Henle (prepared)	A 65-year-old man was just seen recently for fatigue and muscle weakness and found to have a serum magnesium level of 0.6 mg/dL.
Nephron	This should be fun.
Henle (with a curious look)	For 3 days they tried giving him magnesium replacements intravenously and via mouth, and it is improving, but they can't figure out the cause.
Nephron (confused)	Ahhah! This is going be exciting.
Henle	Just some more information, if you allow it, sir.
Nephron	Sure—I hope it is the information I am looking for.
Henle	He really has no significant medical problems except hypertension and gastric reflux disease. His FeMg was 0.5 percent.
Nephron	So it's a gastrointestinal (GI) loss. Why are you bothering me?
Henle	He has no diarrhea, and no apparent GI loss can be found. He has no history of alcohol ingestion.
Nephron (very excited)	Great job; let's move on. So just because there is no GI loss, it is presumed renal losses? You just told me that the kidney is doing the right thing: the urinary loss of magnesium is very minimal. If I had to guess what the urine magnesium was, it must have been very low.
Henle	You are correct.
Nephron	Any other electrolyte problems?
Henle (astounded)	I am getting to that point. Also, hypokalemia and hypocalcemia.
Nephron (calm)	Fascinating!
Henle	So far he is not taking any diuretics, he was not aggressively volume expanded and not hypercalcemic, and I don't see anything on his medication list that can cause renal magnesium wasting, like a chemotherapy agent, calcineurin inhibitors, or amphotericin B.
Nephron	Ridiculous! Why are you even bothered by those things when the kidney is doing the right thing! This is GI loss to me. Please go back and evaluate his medications, and make sure he is not having any GI losses.
Henle exits, and Detective Nephron resumes drinking his coffee.	
Nephron (to himself)	Henle seems to be very puzzled by this one. So far, the kidneys are the smarter organ here!
Before Detective Nephron can go get more coffee, Henle returns to the office.	
Nephron	You're back.
Henle	I am puzzled. His magnesium is persistently low, and his repeat urinary FeMg percent level is appropriately low.
Nephron	Good!
Henle	When we have renal losses, the cause is usually medication, diuretics, certain antibiotics like gentamicin or foscarnet, or primary renal wasting from syndromes. But as you said, it is not a renal cause. He has no diarrhea or pancreatitis, no known or existing malabsorption disease. He has had no known abdominal surgery.
Nephron	Great! The magnesium content of upper GI tract secretions is 15 mEq/L

	compared with 1 mEq/L in the lower tract, so that in general, magnesium depletion due to upper GI tract secretory loss is much more common than that due to lower GI tract disorders. You did some good work. But we still don't have a diagnosis.
Henle	Yes, you are correct.
Nephron (confidently)	Look at his medication list and his known diagnosis. He has hypertension and gastric reflux. What is he taking?
Henle	Metoprolol and omeprazole.
Nephron (chuckling)	All right, then!
Henle	What?
Nephron	Stop the omeprazole, and recheck the magnesium level in a week.
Henle	Really?
Nephron	Yes, proton pump inhibitors (PPI) can cause hypomagnesemia, especially long-term use. Hypomagnesemia in this patient's range, along with hypocalcemia, has been reported in PPI use. Usually the loss is GI, so the urinary magnesium and calcium are low. Hypomagnesemia is associated with hypocalcemia, and this is due to both decreased parathyroid hormone secretion and parathyroid hormone resistance. Hypomagnesemia-induced kaliuresis leading to hypokalemia can be seen with these patients as well. The urinary calcium and potassium in this patient?
Henle	Low and high, respectively. Given the low calcium, his parathyroid hormone was checked, and it is 30 pg/mL.
Nephron	So stop the PPI now!
Henle	Why does this happen?
Nephron (with a smirk)	It is speculated that the drug might interfere with intestinal absorption. Some data say that there might be a renal effect as well. Data from case reports suggest that a renal effect may also contribute. It is possible that the drug interferes with the maximum tubular reabsorption threshold for magnesium.
Henle	This is interesting.
Nephron	Let me know in a week.
Henle exits, and Detective Nephron starts reading ASN Kidney News. A few days later, as the detective is sipping away at his coffee, Henle enters the office.	
Nephron	Nothing is better than a cup of hot coffee! And a great case!
Henle	Once we stopped the PPI and the magnesium, the patient's calcium and potassium all improved slowly. He is being discharged and is asked not to take these agents any more.
Nephron	Great work, Henle. Again, my dear apprentice,from a diagnosis of hypomagnesemia, you found the culprit agent. Always, to be a good detective, observe, think, read, and apply. If it doesn't cross your mind, you will never diagnose it. Great case, Henle. The problem is not always in the kidney!

Hoorne (2010) A case series of proton pump inhibitor-induced hypomagnesemia.

Proton pump inhibitor (PPI)-induced hypomagnesemia has been recognized since 2006. Our aim was to further characterize the clinical consequences and possible mechanisms of this electrolyte disorder using 4 cases. Two men (aged 63 and 81 years) and 2 women (aged 73 and 62 years) had been using a PPI (esomeprazole, pantoprazole, omeprazole, and rabeprazole, 20-40 mg) for 1-13 years. They developed severe hypomagnesemia (magnesium, 0.30 +/- 0.28 mEq/L; reference, 1.40-2.10 mEq/L)

with hypocalcemia (calcium, 6.4 +/- 1.8 mg/dL), relative hypoparathyroidism (parathyroid hormone, 43 +/- 6 pg/mL), and extremely low urinary calcium and magnesium excretion. One patient was admitted with postanoxic encephalopathy after a collapse likely caused by arrhythmia. The others had electrocardiogram abnormalities (prolonged QT interval, ST depression, and U waves). Concomitant hypokalemia (potassium, 2.8 +/- 0.1 mEq/L) was considered the trigger for these arrhythmias. Hypomagnesemia-induced kaliuresis (potassium excretion, 65 +/- 24 mEq/L) was identified as the cause of hypokalemia. This series of PPI-induced hypomagnesemia shows that this is a generic effect. It also indicates that hypomagnesemia may occur within 1 year of PPI therapy initiation and can have serious clinical consequences, likely triggered by the associated hypokalemia. A high index of suspicion is required in PPI users for unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms. (Hoorn et al, 2010b)

Post-marketing pharmacovigilance data review:

Case 1: concerned a 21 year old female patient who started the treatment with oral Pantozol (pantoprazole sodium) with the dose 1200 mg since 12 Dec 2015 to eradicate Helicobacter pylori gastritis. Co-suspect medication included the treatment with Clarithrocin coated tablet 500 mg with the dose 5000 mg since 12 Dec 2015 for Helicobacter pylori gastritis. The patient was underweight with body weight 36 kg and height 158 cm. The patient had intentions for suicide. The eradication therapy had been started by her general practitioner on 11 December 2015, the overdose followed in the night between 11 and 12 December 2015 at around 03:30. The patient had taken 60 tablets of Pantozol 20 mg, 18 tablets of Clarithrocin Mepha Lactab 500 mg and three tablets of Flagyl 500 mg after a dispute, with an intention of committing suicide. At around 04:30, the patient was admitted to the emergency station with tachycardia, rhythmic pulse, ECG: tcSR, heart rate 115 bpm, indifferent type, no ischaemic ST changes, normal de- and re-polarisation, no QTc interval prolongation. During the monitoring of the rhythm (owing to known QTc interval prolongations under clarithromycin), the QTc interval was 530 msec, which was however regressive as shown by regular electrocardiographic controls (measurement on 13 December 2015: 478 msec). The patient's cardiopulmonary state remained stable. There were no indications of cardiac arrhythmias during the 8-hour monitoring. Discharged on 14 December 2015 in fair general condition. No further data can be determined.

Based on the information provided, a causal association between administration of Pantozol and all the reported events cannot be excluded. - CH-TAKEDA-2016TEU000670

Reviewer comment: *There is a temporal association between drug and events and a positive dechallenge. A likely alternative explanation is Clarithromycin over dose, a medicinal product known to prolong the QT interval. Based on the information provided however, a causal association between administration of Pantozol and all the reported events cannot be excluded. Outcome of assessment using French tool is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 2: A 66-year-old Caucasian male presented to the emergency department with non-specific complaints of fever, generalized weakness, fatigue, decreased appetite, diarrhoea and shortness of breath for a week. He had a past medical history of type 2 diabetes mellitus, paroxysmal atrial fibrillation, systolic heart failure, peripheral vascular disease, chronic pain from diabetic neuropathy, dyslipidaemia and hypertension. He was febrile with a temperature of 38.4 degreeC and also had tachycardia with a heart rate ranging from 96 to 137 beats/min. On examination, he had an irregularly irregular pulse and an infected left great toe ulcer. His initial laboratory tests showed a total white blood cell count of 23.5 × 10 3 cells/mm3, with a neutrophil predominance (80% segmented neutrophils, 11% bands). Appropriate cultures were taken prior to initiation of broad-spectrum antibiotics, vancomycin and piperacillin/tazobactam. A transthoracic echocardiogram was performed, which did not show any valvular abnormalities or vegetations related to endocarditis. His ejection fraction was approximately 40%. Prior to admission, the patient had been prescribed atenolol and warfarin for his atrial fibrillation, although his INR was 1.5 upon presentation. At admission, an amiodarone drip was used to control his atrial fibrillation and a heparin drip was initiated for anticoagulation. Digoxin 0.125 mg daily was also started and the atenolol was changed to metoprolol 25 mg twice daily. The patients' other medications included aspirin 81 mg daily, atorvastatin 40 mg daily, lisinopril 20 mg daily and a fentanyl 75 mcg/h patch. The patient's renal function was normal. During Day 6 of his inpatient stay, the patient developed hematochezia and a gastroenterologist was consulted. An esophagogastroduodenoscopy was performed and it was noted that the proximal oesophagus was covered with a white, cheese-like material. The Gram stain revealed budding yeast

and our patient was started on fluconazole 200 mg daily for oesophageal candidiasis. After 2 days of fluconazole therapy (hospital Day 8), the patient was witnessed having a 30-beat run of ventricular fibrillation with a heart rate of 260 beats/min, symptomatic trembling and loss of consciousness. The patient was cardioverted by synchronous electrical shock and transferred to the intensive care unit. The patient's baseline QTc on the day of admission was 365 ms. However, on the day the patient had an episode of ventricular fibrillation, the patient's QTc was 477 ms. The electrocardiogram also showed polymorphic ventricular tachycardia, suggestive of torsades de pointes, which was new compared to previous testing. Cardiology was consulted and they recommended starting intravenous lidocaine and magnesium, and stopping the digoxin. This resulted in the eventual elimination or suppression of the polymorphic ventricular tachycardia. On the day of event, the patient's potassium level was 3.7 mmol/L, whereas his magnesium was 1.9 mg/dL. The antifungal was changed to micafungin 100 mg daily by the infectious diseases service since concomitant use of fluconazole and amiodarone can cause QTc prolongation and cardiac arrhythmias. Antibiotics were changed to cefazolin 2 g every 8 h based on culture and susceptibility results. The lidocaine drip was adjusted based on serum concentrations. On Day 10 of hospital stay, lidocaine was discontinued and amiodarone was changed to oral tablets. On Day 12 of his hospital stay, the patient re-experienced polymorphic ventricular tachycardia. The QTc subsequent to the event was 480 ms, whereas previously it was noted to be 360 ms. Amiodarone and lidocaine drips were restarted, whereas oral amiodarone was held. It was noted that the only new medications since his previous episode of polymorphic ventricular tachycardia were pantoprazole, cefazolin and micafungin. It was decided to stop the micafungin as recommended by the cardiologist. Oral nystatin suspension was used in place of micafungin for the oesophageal thrush. The next day, the patient remained in normal sinus rhythm, the lidocaine was discontinued and amiodarone was switched back to oral tablets. After the micafungin was stopped, the patient did not have any additional episodes of polymorphic ventricular tachycardia while in the hospital despite continuing all other medications. As an explanation, hypokalemia while on an echinocandin could lead to an increased risk of ventricular arrhythmias, but no reports of this have been published with micafungin and our patient had normal serum potassium concentrations throughout the hospital stay. Other than amiodarone and fluconazole, pantoprazole was the only drug the patient was receiving at the time of arrhythmia that has been linked to QTc prolongation. That case was recently reported in a patient with chronic alcohol abuse and resistant hypomagnesaemia. This scenario does not appear likely in our patient as his magnesium concentration was within normal limits and he was not dependent on alcohol. Although the long elimination half-lives of fluconazole and amiodarone may have contributed to the event repeating itself, use of the Naranjo adverse drug reaction probability score indicates a possible relationship between the polymorphic ventricular tachycardia and micafungin therapy in this case. WHAT IS NEW AND Conclusion: This is the first report of a patient with polymorphic ventricular tachycardia suggestive of torsades with micafungin as a possible cause. Although this adverse event is rare and is usually seen in patients with both multiple comorbidities and medications that may increase the risk, it can be fatal if undiagnosed. Healthcare providers must be aware of this possibility, especially when switching from an azole antifungal to an echinocandin to avoid drug interactions, and should closely monitor patients if they are on other medications that could contribute to the development of polymorphic ventricular tachycardia.US-EMA-20160622-AUTODUP-466281

Reviewer comment: *Based on the temporal association and known drugs safety profile, a possible contribution of the drugs amiodarone and fluconazole to the development of events can't be excluded in context of an interaction. Micafungin provided an alternative explanation to the second episode of arrhythmia events. A causal role of pantoprazole would seem unlikely in this case since the patient did not have any additional episodes of polymorphic ventricular tachycardia while in the hospital despite continuing the drug.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R-	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 3: 55-year-old female patient who developed macroscopic T-wave alternans and QT prolongation (unusual companions) subsequent to medication use. Metronidazole was recieved in this patient for clostridium difficile colitis as well as pantoprazole. She had COPD (Chronic obstructive pulmonary disease), clostridium difficile colitis, alcohol abuse and tobacco abuse was admitted for hyponatremia and necrotizing pneumonia. On an unreported date, at admission the patient received antibiotics included ceftriaxone, vancomycin, and unspecified metronidazole for clostridium difficile colitis. Echocardiography (echo) showed a 20% ejection fraction (EF) with wall motion suggestive of stress cardiomyopathy. Electrocardiogram (ECG) showed sinus tachycardia with QS in the precordial leads. On an unreported date, after six days, the patient developed new QT-prolongation and macroscopic T-wave alternans (MTWA) with negative troponins. The patient also received following drugs aspirin, metoprolol, lisinopril, cefepime, atorvastatin, pantoprazole, and heparin. Potassium was 2.9 mEq/L and magnesium was 1.6 mEq/L. Electrolytes were repleted and patient was stopped metronidazole and pantoprazole therapies. Electrocardiogram (ECG) showed QTc improved, MTWA disappeared, but diffuse T-wave inversions remained. No arrhythmias occurred and the EF improved to 45% on repeat echocardiography. US-BAXTER-2016BAX038846

Reviewer comment: *There is a temporal association between drug with the QT interval prolongation There is also a positive dechallenge. However a more likely explanation would be the depleated electrolytes, ie. hypokalaemia which naturally follows episodes of hyponatraemia.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatable
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 4: This study case was reported in the medical literature by a physician from Australia and concerns a 66-years-old male patient who experienced a serious adverse reactions of intoxicated and postural hypotension associated with escitalopram, perindopril, atenolol, rosuvastatin, pantoprazole, and lercanidipine, serious adverse reactions of hypokalaemia and drug induced QT prolongation, and non-serious adverse reaction of hypomagnesaemia associated with escitalopram. The patient had the medical history of Hypertension, alcohol dependence, liver cirrhosis, and hypercholesterolaemia. The patient was treated with perindopril, atenolol, rosuvastatin, pantoprazole, lercanidipine, and escitalopram (10 mg daily) for an unknown indication. The patient was admitted to the hospital due to intoxicated with postural hypotension. The patient also had hypokalaemia (with potassium value 3.0), hypomagnesaemia (with magnesium value 0.56), and drug induced QT wave prolongation. On electrocardiogram QT interval showed 440 and heart rate 106. This adverse reaction was considered serious: hospitalization and medically significant. AU-EMA-20160808-ashishvp-100016638

Reviewer comment: *There is a temporal association between drug and but multiple other drugs are involved including escitalopram, well known to cause diQT prolongation as well as hypokalaemia. Furthermore a higher risk of QT prolongation and sudden cardiac death has been demonstrated in patients with alcoholic liver disease* (Campbell, 1993).

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatable
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1

Result	I1	Uncertain

Case 5: concerning a female (age unknown) who was administered Protonix(R) (pantoprazole) injection- in the treatment of GI bleeding. Medical history was not provided. It is unknown if the patient was taking concomitant therapy. The reporter stated that the patient experienced a prolonged QT interval of 599ms coincident with Protonix i.v. therapy. When intravenous treatment was completed the QT-interval returned to normal. She received pantoprazole intravenously for 3 days for the treatment of gastrointestinal hemorrhage. Her treating physician reported prolongation of the QT interval on ECG which occurred on the second day of treatment and had apparently resolved by the time an ECG was taken on the following day. Further information is expected. The physician reported the treatment period as approximately 26 until 28Jan02. USPFIZERINC-2002095490US

Reviewer comment: *Temporality is compatible in this case. There is very little information to assess this case. Outcome using French tool is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 6: concerns a 40 year-old female hospital patient on cisapride who, on day 2 (28-Jun-1998) postop elective laproscopic cholecystectomy,suddenly began experiencing seizure, QT prolonged (0.40 seconds), cardiac arrest, Torsade de Pointes, and hypokalemia (3.0 mmol/L). These events were severe and cisapride was discontinued. In the outcome, the patient recovered with residual effects. The health professional reporter believes the cardiac arrest is secondary to the cisapride and pantoprazole, while the hypokalemia is secondary to the indapamide (the patient had been on all 3 drugs for an unspecified time prior to hospital admission). When physicians were doing rounds patient became presyncopal BP went from 90/50 to 140/80 lying down, HR 72. Patient felt tingly, experienced a 30 second tonic seizure that resolved spontaneously. ECG was performed showing Torsade de Pointes, patient then became pulseless and was bolused with 1 g MgSO4. Torsades continued then bolused with lidocaine 1 g then an infusion was started. A few minutes later patient was arrested in ventricular fibrillation and was defibrillated with 200 joules x 1 and converted to sinus rhythm then bolused with 1 g MgSO4. Potassium level taken during this episode was 2.1 mmol/L. Patient prior to surgery was discovered to have low potassium and magnesium levels and levels were corrected prior to procedure. Due to unusual low levels workup was initiated for underlying cause. CT scan of the adrenals showed a 4 mm left adrenal mass. Pending conclusion was hyperaldosteronism. Further tests to be performed on an outpatient basis. Includes: hypertension, GERD secondary to biliary colic. Vague family history of palpitations and increased heart rate. CA-JNJFOC-JAOCAN2000000455

Reviewer comment: *A temporal relationship exists. However the hypokalemia experienced due to underlying disease (hyperaldosternosim) as well as the concomitant administration of cisapride provided more likely explanations for QT prolongation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 7: case regarding a 31-year-old female patient who received Pantozol (pantoprazole tablet, delayed release) therapy and intentionally ingested 7 tablets of Pantozol, as well as ibuprofen, butylscopolamine and paracetamol in a suicide attempt. The patient developed slightly prolonged QT interval and tachycardia. Additionally, the patient experienced nausea and hypokalemia. The patient's concurrent illness includes iron deficiency anaemia. The patient was treated with acetylcysteine and regular laboratory controls were performed. In follow-up information received, it was reported that except for moderate nausea, the patient complained of no other symptoms. The patient was hospitalized for 1 day. Laboratory tests showed hypokalaemia and the ECG was found without significant repolarization disorder DE-Nycomed-0213286

Reviewer comment: *A temporal relationship exists. However hypokalemia experienced provides a more likely explanations for QT prolongation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 8: Case regarding a 91-year-old female patient who received Cordarone (amiodarone unspec) therapy and experienced torsade de pointe, electrocardiogram QT prolonged, supraventricular extrasystoles, hypokalemia and hypertension. The patient's concurrent illnesses include atrial fibrillation (chronic),coronary artery disease, hypertension, hypothyroidism and myocardial ischaemia. Additional suspect medication included Metoprolol, Lisinopril, Furosemide, Lormetazepam, Levothyroxine and Pantozol (pantoprazole unspec). The patient experienced torsade de pointe (torsade de pointes), electrocardiogram QT prolonged (electrocardiogram QT prolonged), hypertension (hypertension), supraventricular extrasystoles (supraventricular extrasystoles) and hypokalemia (hypokalaemia). The patient was admitted to the cardiology unit because of syncope-at-rest, accompanied with a short period of loss-of-consciousness. Blood pressure was 210/100 mmHg and heart rate was abnormal at 48 bpm. On auscultation a systolic murmur was diagnosed. Laboratory testing revealed hypokalemia at 2.4 mmol/L. On ECG there was initially a ventricular bigeminia and a prolonged QT-PR interval; during monitoring later on, a torsade de pointe was diagnosed. Echocardiography showed a sclerosis of the aortic valve with a moderate gradient of stenosis and a moderate aortic valve insufficiency. The cause of syncope was diagnosed as the presence of torsade de pointe caused on "one hand" by amiodarone use and "on the other hand" by hypokalemia due to furosemide. Corrective treatment included potassium and magnesium; additionally amiodarone was stopped. Serum potassium levels normalized after 2 days. The QT interval prolongation persisted on the ECG, probably caused by amiodarone impregnation. Amlodipine was added to the medication for a better blood pressure control. Torsade de pointes, hypertension and hypokalemia were also considered life-threatening. The outcome of torsade de pointe, hypertension and supraventricular extrasystoles was unknown. BE-WYE-H01064107

Reviewer comment: *Temporal relationship, no alternate explanation. Fexofenadine at suprathereutic doses was not seen to prolong the QT interval in through QT study with fexofenadine (as per SmPC). Hypokalaemia was also present in this patient may have caused the QT interval prolongation and subsequent TdP. Causality assessed as Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 9: concerns a patient diagnosed with prostate cancer in 1998. He initially underwent a transurethral resection of the prostate and bilateral orchiectomy. One year later he was found to have metastatic disease in the retroperitoneum, vertebrae, femurs, and skull that was refractory to treatment with bicalutamide and leuprolide. He had recently begun treatment with estramustine and taxotere. Seven days after receiving a single IV dose of zoledronate 4 mg for bony pain related to metastatic prostate cancer, the patient presented to the emergency room with complaints of nausea and dysphagia. Physical examination was remarkable for a positive Trousseau sign and laryngeal spasm. The ECG showed a prolonged QT interval (QTc = 559 ms). Laboratory studies revealed profound hypocalcemia, with an albumin-corrected serum calcium of 5.4 mg/dL. Laboratory data were also remarkable for hypophosphatemia of 2.2 mg/dL. Serum 25-hydroxyvitamin D concentration was 9 ng/dL which was consistent with severe vitamin D deficiency. The markedly elevated serum PTH concentration (174 pg/dL) indicated secondary hyperparathyroidism. During the first 24 hours after admission, the patient received a total of 18 ampoules of IV calcium gluconate with resolution of his tetany and normalisation of his ECG. He was started on oral calcium and 1,25 dihydroxyvitamin D. The proton pump inhibitor (pantoprazole) was stopped to increase gastric acidity and improve intestinal calcium absorption. Despite these measures, the patient required continuous slow infusion of calcium gluconate for an additional 16 days in order to maintain serum calcium levels above 7.0 mg/dL. The patient was discharged on oral parent vitamin D and Citracal plus. One month later, his serum calcium was 8.2 mg/dL. The authors stated that this patient had several risk factors for developing severe hypocalcemia after therapy with zoledronate. In addition to severe vitamin D deficiency, achlorhydria secondary to gastric surgery, and proton pump inhibitor use may also have limitied intestinal calcium absorption, as optimal absorption of calcium requires gastric acid. He also had extensive osteoblastic metastases and may have been depositing calcium into these lesions. All of these factors may have limited his ability to mobilize skeletal calcium into the serum, a situation that would have been greatly exacerbated by the zoledronate. neoplasm of the prostate diagnosed in 1998, hyperplasia of prostate, malignant neoplasm of stomach, essential hypertension, transurethral resection of prostate, bilateral orchiectomy, gastric surgery, and achlorhydria. Achlorhydria secondary to gastric surgery, extensive osteoblastic metastases with deposition of calcium into these lesions] provide a possible explanation for the reported adverse event. All literature reports are considered suspected for reporting purposes. US-EMA-20111110-mkevhumanwt-104352020

Reviewer comment: *Temporal relationship exists, but there are many other alternate explanations eg. profound hypocalcemia, as described by the reporters. Causality assessment judged as Uncertain using the French method.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 10: concerns a patient with a mitral cusp defect diagnosed in his youth and with various neurocirculatory-type complaints (anxiety, palpitations, and pain in the heart region) was managed effectively with metoprolol. On account of recently diagnosed oesophageal reflux disease his gastrologist had prescribed pantoprazole 20mg twice daily, and this treatment happened to coincide with an ECG checkup carried out as part of the patient's regular monitoring. The recording was "almost" normal, apart from the QRS complexes over the inferior wall and the rather unusual configuration of the ST-T complexes in leads V2 and V3. An artefact was initially suspected, and the patient was instructed to have a repeat ECG within the next few days, but the recording remained unchanged. In this undulating region in the ventricular repolarization phase there was a convex elevation of the ST segments from the J point, differing decisively from a picture of early ventricular repolarization and a U wave superimposed onto an untypically long descending arm of the T wave. The QTU interval in leads V2 and V3 measures 0.54 sec (and after a Bazett correction relative to the RR interval lasting 0.9 sec it is 0.57sec). In point of fact it was not easy to compare these values with

the QT intervals in the remaining leads without U waves, because such dispersion of repolarization was of course difficult to interpret, and also because there were no "standards" for QTU intervals in the situation in which U was superimposed on T, since the very occurrence of such superimposition was pathological. On the other hand, it was worth trying to determine the QT interval in these leads by the generally recommended method, i.e. by constructing a tangent to the descending arm of the T wave and taking the point of intersection of this tangent with the isoelectic line as the end of the T wave. When this was done it was found that, on account of the slope of this arm, which was less steep than usual, the end of the T wave occurred not much nearer than the end of the U wave. There was therefore every reason to interpret this unusual picture as a ventricular repolarization disturbance of the type that showed a long QT interval. After discontinuation of pantoprazole, the described ST-T changes disappeared. PL-EMA-20120110-tkaurp-130345992

Reviewer comment: *This case has a suggestive temporal relationship as well as a clear dechallenge.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	*Compatible*
Rechallenge	R0	Lab Test	*L0*
Dechallenge	C2	Alternate	*S2*
Result	I2	Possible	

Case 11: concerns a female patient who started therapy with pantoprazole. Co-suspect medication included fingolimod, 0.5 mg once daily, oral, started in 2011 for multiple sclerosis. No other medical history and no concomitant medication were reported. On an unknown date after the first dose of pantoprazole), the patient developed slight tachycardia at 73 bpm and QT prolongation of 418 ms and "QT ca 115%" with slight bundle branch block. A control investigation confirmed the results. Therapy with fingolimod was discontinued in AUG-2012 after approximately one year of treatment. Action taken with pantoprazole was not reported. Outcome of the adverse reactions was not reported. - *002147023-PHHY2012DE105858*

Reviewer comment: *Temporal relationship exists however the use of co-suspect fingolimod provides a more plausible alternative explanation for the occurrence of the reactions in this patient.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 12: concerns an 84-years old female patient started to receive venlafaxine (EFEXOR) orally on an unknown date at 75mg once daily for an unknown indication and pantoprazole (PANTOZOL) orally at 40mg twice daily for an unknown indication. Relevant concomitant medications included phenprocoumon (MARCOUMAR) orally, hydrochlorothiazide/Enalapril maleate, metoprololsuccinate (METO ZEROK) orally at 12.5mg once daily and lorazepam (TEMESTA) Relevant medical history included chronic renal insufficiency with nephroangiosclerosis, anxiety and depressive disorder, hypertensive cardiac arrhythmia with atrial fibrillation and persistent normal-tachycardia in 2007. On 23Feb2011 the patient was hospitalized due to atrial fibrillation with low ventricular response with a QT prolonged and torsade de pointes. It was found a hypomagnesaemia with a magnesium value of 0.59 mmol/l (reference range: 0.65-1.05) which was a possible factor for the QT prolongation which

was possibly related to the stopped venlafaxine therapy on 23Feb2011. The calcium value was in normal range. The patient received a magnesium supplementation. The concomitant medication metoprolol was withdrawn on 23Feb2011 and replaced by Isoprenalin (ISUPREL) for 12 hours. It was reported that at the moment an insertion of pacemaker was not proposed due to favorable clinical course and patient's general condition. CH-EMA-20130128-mgevhumanwt-153127103

Reviewer comment: *A temporal relationship exists however the patient had other risk factors that may have contributed to the development of hypomagnesaemia, e.g. co-suspect venlafaxine, concomitant metoprolol and concurrent concomitant hydrochlorothiazide/enalapril.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 13: concerns a 48-year-old female patient from Germany. On 04-SEP-2012, the patient had attempted suicide by administering pipamperone promethazine hydrochloride (unspecified, oral), olanzapine (unspecified, oral), venlafaxine (unspecified, oral), and pantoprazole sodium (unspecified, oral). It was not known whether pipamperone was prescribed routinely. The reporter stated that, after intake of the drugs the patient experienced somnolence, tachycardia 130 to 140 and agitation. Other suspect drugs included ethanol for an unspecified indication. On 04-SEP-2012, the patient experienced prolongation of qt interval and increased creatine kinase level. Laboratory data included alcohol 1.2 per mille (sic) and creatine kinase (CK) 1784 IU/L.The patient recovered from suicide attempt, creatine kinase increased, prolongation of qt interval, agitation, somnolence and tachycardia at the time of this report. The patient's medical history and concurrent conditions included agoraphobia, borderline disorder, had experienced several previous suicide attempts according to relatives, but patient did not talk about the suicide attempt and panic attack. The patient had a history of alcohol abuse. It was stated that patient was already prescribed with pipamperone long before she was admitted to the intensive care unit and suspected indication for use of pipamperone was panic attacks. DE-JNJFOC-20120901397

Reviewer comment: *Temporal relationship exists however other alternative explanations such as concomitant pipamperone, promethiazine and venlafaxine provide a more plausible explanation for QT prolongation in this patient.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 14: Patient 89 years, 52 kg / 1.58 m, who has type II diabetes treated by diet alone, hypertension, hiatal hernia (and esophagitis Ulcerated, diagnosed in February 2012) and vertebral settlement. Chronic treatment included Forstéo®, Kardégic® 75Mg / d, Cacit D3®, pantoprazole 20 mg / d, paracetamol codeine, Tanganil® for dizziness. Episode of Gastroenteritis a few days before admission. 31/01/13: hospitalization for convulsive seizures on severe hypocalcemia (Ca = 1.02 mmol / l, protein 54 g / l, albumin = 29 g / l). Extension of QT to The ECG (corrected QT 491 ms). The patient is also deficient in magnesium (Mg = 0.32 mmol / l, 0.7 in iron (iron = 7 µmol / l, saturation coefficient = 13%, 13 µg / l, 10 µmol / l normal) In vitro B12 (<111 pmol / l, 142 (25-OH-vitD <12.5 nmol / l, 75

anemia (Hb 101 g / l) microcytic (GMV = 74.7 fl) Creatinine clearance at 73 Ml / min. Discreet inflammatory syndrome (CRP 14 mg / l). High PTH = 171 pg / ml (11.5 Treatment: calcium IV and calcium, vitamin D, iron and magnesium. She returned home on 13/02/13 with change of IPP for esomeprazole, Supplementation with vitamin D, calcium, Magne B6, vitamin B12 and Fortimel®. FR-AFSSAPS-TS20130105

Reviewer comment: *In all, symptomatic hypocalcemia with convulsive seizures and prolonged QT in a context of hypomagnesemia, vitamin D deficiency, anemia Iron deficiency and vitamin B12 deficiency, during treatment with Pantoprazole and Forstéo® in an 89-year-old patient. Apart from adverse event hypomagnesiaemia, the above provide more plausible explanations for the event then administration of pantoprazole.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 15: Case concerns patient with a background of alcoholic cirrhosis (Child A, Grade 2 esophageal varices) asymptomatic hyperuricemia. On 8/05/2013: hospitalized for trouble of rhythm: tachycardia at 120 btm / min, Sinus rhythm, long QT and short PR Biology: cytolysis TSH: 4.47 mIU / L

Reviewer comment: *Not assessable*

Case 16: concerns a 53-year-old male patient who received Pantoprazole for peptic ulcer prophylaxis. Concurrent medical conditions included chronic alcohol abuse. The patient had no previous cardiac history. On an unknown date the patient was brought by Emergency Medical Services with a chief complaint of palpitations and dizziness for 1 day. His only significant medical history was chronic alcohol abuse and was not taking any medications before his admission. His physical examination was normal, except for an irregularly irregular rapid pulse and a blood pressure of 157/104 mm Hg. The ECG on admission showed atrial fibrillation with rapid ventricular response at an average of 190 beats per minute. Admitting routine labs showed normal complete blood counts. Electrolyte laboratory values revealed 136 mEq/L of sodium, 4.6 mmol/L of potassium, 100 mEq/L of chloride 16 mEq/L of bicarbonate, 11 mg/dL of blood urea nitrogen, 0.68 mg/dL of creatinine, 9 mg/dL of calcium, and 1.5 mg/ dL of magnesium. He was started on intravenous diltiazem for rate control and intravenous heparin for anticoagulation. Routine oral pantoprazole 40 mg once daily was prescribed for peptic ulcer prophylaxis. Seven hours later, while on telemetry, the patient became unresponsive. The telemetry rhythm strip showed sustained polymorphic ventricular tachycardia (pVT). The patient was treated with 1 g of IV magnesium sulfate, IV lidocaine bolus of 100 mg, and maintenance of 1 mg/min infusion, followed by 3 successive cardioversions, which eventually restored sinus rhythm. Another 2 g of magnesium sulfate was administered intravenously, and the patient was intubated for airway protection. After successful cardioversion, a 12-lead ECG showed sinus rhythm at 95 beats per minute, with T wave alternans. The measured QT was 0.62 s (QTc = 0.65 s), alternating with 0.46 s (QTc = 0.51s). During his hospital stay (41 days), the patient was maintained on IV lidocaine at 2 mg/min, as well as IV magnesium for replacement (up to 6 g of magnesium sulfate per day). Despite the daily high doses of magnesium administered, the serum level fluctuated from 1.5 mg/dL to 2.7 mg/dL, and the QTc remained prolonged varying from 0.47 to 0.72 s (average of 0.538 plus/minus 0.062 s). Incessant sustained and nonsustained episodes of pVT and torsades de pointes continued to occur over the span of 16 days, requiring another 6 direct current cardioversions during this period. These episodes of pVT were always heralded by marked QTc prolongation, with a range of 0.55 s to 0.72 s. The patient was still receiving 40 mg of pantoprazole daily. A 24-hour urine magnesium showed a urinary loss of 13.5 mg/dL. On day 16 of admission, pantoprazole was discontinued. Three days after

the cessation of pantoprazole, the QTc shortened to a daily average of 0.457 plus/minus 0.0275 s until the day of discharg. Together with the shortening of the QT interval, the daily requirements of magnesium supplementation were significantly reduced to an average of 2 g per day. There were no recurrences of pVT or TdP after the discontinuation of pantoprazole. Coronary angiography was also performed during this admission, and it showed no coronary artery disease. Follow-up after 1 month showed a normal ECG with a QTc of 0.38s. Patient remains well during his 1-year follow-up. The author considered the events were life threatening and clinically significant (or requiring intervention). Treatment with Pantoprazole was discontinued. At the time of reporting, the events were resolved. The author considered the events were related to treatment with Pantoprazole and stated "we conclude that the addition of a PPI, which is the standard of care in critically ill patients, should be used with caution in patients who have a previous tendency to hypomagnesemia, as in our patient. In these patients, PPIs can potentiate the hypomagnesemia-induced lethal arrhythmias, which can result in sudden cardiac death. PPI therapy can potentially be dangerous in critically ill patients who are prone to electrolyte and nutritional abnormalities. US-GlaxoSmithKline-B0901228A

Reviewer comment: *A plausible temporal relationship exists with a positive dechallenge. Of note is that the presenting complaint, suggestive of heart disease which could be an alternate explanation for the events although this does not seem likely considering the evolution of this case. With regard to the co-suspect medication diltiazem, the events QT prolongation or hypomagenasemia are both not listed events. The contributory role of pantoprazole in inducing hypomagnesiaemia with subsequent QT prolongation seems very plausible in this case, potentiated by the fact that chronic alcoholism can cause serious magnesium deficieny* (Flink, 1986).

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S1
Result	I3	Probable	

Case 17: IT-MINISAL02-221280 – not assessable

Case 18: concerns 68-year-old female patient with pyrosis who started treatment with oral pantoprazole 40 mg tablet twice daily, from an unknown date in 2005. On an unknown date in 2013, 8 years after administration of pantoprazole, the patient experienced QT interval prolongation. On 18-Oct-2013, the therapy with pantoprazole was discontinued. On an unknown date in Oct-2013, the patient had recovered from QT interval prolongation. The outcome of the case was "recovered". The causality per reporter for pantoprazole was not reported. NL-AUROBINDO-AUR-APL-2013-09265

Reviewer comment: *The latency period between drug and event precludes any meaningful assessment of this case.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Impossible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C0	Alternate	S1
Result	I0	Unlikely	

Case 19: A 73-year-old female was admitted to hospital with cerebovascular infarction. Patient history revealed replacement of the mitral valve with a mechanical valve, atrial fibrillation, suspected pre-

existing prolongation of QT-interval. On an unknown date therapy with ZacPac (combination of pantoprazole, amoxicilline and clarithromycine) was started for treatment of duodenal ulcer including eradication of Helicobacter pylori. One g of Clarithromycine (within the combination product ZacPac) was applied p.o. until the 13-Dec-2005 (starting day not specified) and one dose of Clarithromycin (Klacid) was applied i.v. on the 14-Dec-2005 with an unknown stop-date, when the patient suffered from fever and signs and symptoms of cerebral infarction. Patient did not receive clarithromycine before. Co-medication included ethyldigoxin q.d., lisinoprile 20 mg q.d., verapamil 240 mg q.d., hydrochlorothiazide 12.5 mg q.d. and enoxaparine s.c. 0.6 ml b.i.d. On the 15-Dec-2005 the patient needed cardiopulmonary resuscitation due to life-threatening ventricular fibrillation and prolonged QT-interval. The reporter suspected a prolongation of a pre-existing prolonged QT-interval due to the macrolid antibiotic. The suspected medication was stopped and no new signs of heart rhythm disorder reappeared. The outcome was reported as with no persistent disability, ECG revealed long QT-interval with T-U wave (afterdepolarization). ZacPac contains pantoprazole, amoxicillin and clarithromycin as separate tablets in a blister pack. Each blister provides tablets for one day, according to the recommended regimen for H. pylori eradication: pantoprazole 40mg bid, amoxicillin 1000mg bid, clarithromycin 500mg bid. From the medical history it is obvious that this patient suffered from severe cardiovascular disease: atrial fibrillation and prolonged QT-interval were pre-existing conditions in this elderly patient and a variety of concomitant drugs were reported for treatment of that condition. Due to cerebrovascular infarction, the patient was admitted to hospital. The start date of ZacPac is not reported; ZacPac was stopped 13-Dec-2005 and replaced by Clarithromycin i.v. on the 14-Dec-2005 due to fever. On the 15-Dec-2006 the patient suffered from life-threatening ventricular fibrillation requiring CPR. Following stop of Clarithromycin i.v. and ZacPac, no reappearance of cardiac rhythm disorder was reported. The patient recovered completely. Despite only limited information regarding exposition of the patient to ZacPac, Altana Pharma assesses the event 'prolongation of QT-Interval' as possibly related to ZacPac. Since this event led to ventricular fibrillation and CPR, also these events will be assessed as possibly related to ZacPac. Prolongation of QT-interval and ventricular tachycardia are rare, but labeled adverse reactions to ZacPac. Therefore, this report is not considered to have any influence on current knowledge regarding the safety profile of ZacPac.

Reviewer comment: *A temporal relationship is present and a positive dechallenge. However, it is more likely that the QT interval prolongation and subsequent arrhythmia was a result of the clarithromycin component rather than pantoprazole.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 20: This patient had taken pantoprazole (tablet, delayed release) 40 mg daily for two days as gastrointestinal prophylaxis. Medical history included coronary artery disease. Concomitant therapy included Plavix (clopidogrel) and possibly other unspecified medications. While hospitalized, patient underwent cardiac catheterization, thallium scintygraphy and electrocardiography. She was noted to have QT-prolongation on the monitor. Protonix was discontinued immediately and the QT interval returned to normal. The patient's experience reportedly prolonged their hospitalization. This patient has a history of coronary artery disease for which several investigations has been carried out. The patient's cardiac condition might well have played a role in the development of the described QT-prolongation. Several studies have been performed in which by monitoring heart rate, blood pressure and the performance of ECGs an influence of pantoprazole on cardiovascular function could be excluded. US-EMA-20140604-rhandoop-104155198

Reviewer comment: *In this case,the underlying disease for which she was being investigated is a more likely cause of the QT interval prolongation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 21: This case concerns a 51 years old female patient who experienced recurrent proton pump inhibitor-induced hypomagnesemia (0.06 mmol/l) after two weeks of starting therapy with pantoprazole and after few years of starting therapy with omeprazole. The patient had a medical history of parathyroidectomy (two years previously) for primary hyperparathyroidism due to adenoma. Her concurrent conditions included hypokalemia, hypocalcemia, prolonged QT interval and Zollinger-Ellison syndrome. Concomitant medication included amlodipine for arterial hypertension. No past drugs were reported. On an unspecified date the patient stated receiving therapy with omeprazole a 40 mg daily (route and form not reported) for peptic ulcer disease. She continued receiving the drug for two years. On an unknown date, few years after initiating therapy with omeprazole, she was hospitalized because of general seizures and severe hypomagnesaemia with a serum magnesium level of 0.06 mmol/L (normal: 0.7-1.05 mmol/L). She was given magnesium replacement therapy, but hypomagnesaemia persisted. Ten weeks later her serum magnesium level was at 0.31 mmol/L. On an unknown date she developed vomiting and diarrhea that continued for two weeks. Two weeks later, she presented to the hospital with acute confusion, ataxia, carpopedal spasm, intermittent downbeat nystagmus and serum magnesium level of 0.07 mmol/L. The next day she was admitted to a tertiary hospital and the magnesium level was at 0.41 mmol/L. Fractional excretion of magnesium was low at 0.40% and urine magnesium was 0.53 mmol/l. Given its suspected causal role, omeprazole therapy was discontinued. An increase in serum magnesium levels was subsequently seen on a short term period, without the need for further magnesium replacement. A complete neurological recovery was observed after correction of the ionic disorders. Ten days later she had a severe upper gastrointestinal bleeding due to peptic ulcer disease, leading to re-initiation of proton pump inhibitor therapy with pantoprazole at 40 mg daily (route and form not reported) for peptic ulcer disease. Two weeks later a blood test showed a relapse of hypomagnesaemia. Pantoprazole was stopped and ranitidine was prescribed. A few days later gastrointestinal bleeding recurred. Subsequently she was treated successfully with a combination of ranitidine and octreotide. Since then magnesium level remained normal without substitution therapy. Action taken: Therapy discontinuation BE-EMA-20140909-abhogalp-143605672

Reviewer comment: *In this case, considering compatible drug-event temporal relationship, the role of pantoprazole and omeprazole cannot be denied for the event of hypomagnesemia; however, their individual roles cannot be assessed in isolation. Furthermore, her concurrent conditions included hypokalemia, and hypocalcaemia which are strong risk factors to the development of QT interval prolongation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Active substance	BH criterium	Assessment
Pantoprazole	Strength of association	1.00 PRR, 19 ADR Case reports majority of which causality uncertain. No new articles (other than those in eudravigilance) were identified in literature. 3 case reports were retrieved for PPI association with hypokalaemia.
	Biological Plausibility	The preclinical data submitted in this generic dossier was insufficient to characterise any effects on hERG. In the literature 2 indirect mechanisms have been postulated for effect of hypokalaemia (a risk factor for QT interval prolongation) 1. via hypomagnaesemia induced kaliuresis (Bibawy et al, April 2013) (Hoorn et al, 2010a) 2. via the effect of on the inward rectification of the potassium channels (IKr) by plugging the opened channels as well as modulating the outwardly directed potassium current (Ito). (Bibawy et al, April 2013)
	Biological gradient	Increased QT interval prolongation was not observed with increasing dose of pantoprazole
	Experimental evidence and temporality	Of the 19 cases assessed for QT prolongation, all but 1 had a temporal relationship between the events and the initiation of treatment. Most cases were confounded by other drugs or presence of electrolyte imbalances and some occurred in the presence of underlying cardiac conditions. The majority of cases were assessed as having an Uncertain or Unlikely causality.
	Consistency	The presence of electrolyte imbalances was seen commonly when assesseing the cases and from literature review. It appears that PPIs cause electrolyte imbalances which have a cascading effects.
	Specificity	In preclinical data the block on hERG potassium channel if any was not studied.
	Analogy	The other PPIs do not carry a warning for QT interval prolongation or hypokalaemia.

Overall assessment	***In the Eudravigilance database the association of pantoprazole with QT prolongation was disproportionally reported for this drug over others. Literature and case review do not support a direct relation between drug and effect, and preclinical data did not demonstrates a direct mechanism of action. There is reason to believe however, that PPIs are causing hypokalemia as a result of hypomagnesaemia or due to gastric loss from their action on H+/K+/ATPase. The through analysis of PPIs and hypokalaemia should be investigated separately.***
Benefit Risk Balance	*The benefit risk balance of this product remains positive.*

Appendix 5:
Dexmedetomidine

Malta, January2017

Signal Description Message

From	To	Copy to
Amy Tanti	Post-Licensing Directorate	Professor John J Borg

Subject

Medicinal product	Dexmedetomidine DEXDOR
Signal (MedDRA term)	Electrocardiogram QT interval prolonged

Priority Grade Proposal:

Important risk

Summary

Imputability Score	**Number of case**
I4-Highly Probable	0
I3-Probable	2
I2-Possible	0
I1-Uncertain	6
I0 -Unlikely	0

Signal characteristics

Source (database, literature…)	Eudravigilance database, medical literature, company clinical and pre-clinical data
Number of reports	8 unique ICSRs, 1 EU, 7 Non-EU.
Expectedness	No
Seriousness	Yes Drug induced QT interval prolongation predisposes to arrhythmias, including the lethal Torsade de Pointes.
Statistics (if available, e.g. PRR, IC, confidence interval…)	

Reaction PT	PRR (-)	PRR	PRR (+)	Static PRR Analysis - CHI^2
Electrocardiogram QT prolonged	2.666269429	4.9377128	9.14424	31.45318346

Dexmedetomidine: Dexdor® 100 micrograms/ml concentrate for solution for infusion

Mechanism of action: Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised.

Date EU approval: 16th September 2011

Indication: For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

Availability in MT: not available on the GFL

Currently authorised SmPC wording:

Section	Wording
4.3 Contraindications	Not listed
4.4 Warnings	Not listed
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

Number of reports in Eudravigilance database: 8 unique, 1 EU, 7 Non-EU.

Summary of company preclinical data

The cardiovascular effects and safety of dexmedetomidine was studied in different species and under various conditions, including conscious and anaesthetized animals.
Heart rate, myocardial contractility, oxygen demand and cardiac output were all reduced in response to dexmedetomidine. The responses to rapid i.v. injection of doses ⩾ 0.3-1 μg/kg are transient increases in blood pressure due to increased peripheral alpha-2 adrenoreceptor-mediated vascular resistance and compensatory decreases in heart rate. These are followed by central alpha-2 adrenoreceptor-mediated, more sustained decreases in both blood pressure and heart rate. If the dose is given more slowly (i.m. or i.v. infusion), the initial increase in blood pressure is absent or small. Importantly, despite the reduced cardiac output, sufficient perfusion of the vital organs seems to be maintained, especially when oxygen demands are simultaneously decreased.

Proarrhythmic potential

Dexmedetomidine and the H-3 metabolite are very poor hERG blockers in stably transfected HEK cells. The test system was validated with a positive control substance E-4031 which was shown to be a potent hERG blocker as described in the literature. The EC50 value of dexmedetomidine for activating the human alpha-2 adrenoceptor is around 1 nM, resulting in hERG IC50/alpha-2 adrenergic receptor EC50 ratio of 30 000. This is 2-3 orders of magnitude higher than the safety margin of 30-100 which has been suggested to be adequate to ensure an acceptable degree of margin for the absence of arrhythmogenesis in man (Redfern WS et al., 2003). The therapeutic free plasma concentrations of dexmedetomidine in humans are in the nM range (e.g. at a target plasma level of 2.5 ng/ml the protein free fraction is 0.15 ng/ml/0.6 nM). A very high in vivo cardiac safety index (hERG IC50/free therapeutic maximum plasma concentration) for dexmedetomidine is thus also apparent. Similar high safety margins appear to hold also concerning the tested major human metabolites (G-Dex and H-3).

In the dog Purkinje fiber assay (TDPscreenTM)), dexmedetomidine (1 μM) induced a slight increase in APD but categorized to compounds which cause TdP only in very rare cases. Other compounds with a similar ranking include e.g. risperidone, ondansetron and fluoxetine which have not shown any proarrhythmic problems despite their wide clinical use. The TDPscreen algorithm is based on APD prolongation and some other electrophysiological effects of the compound (triangulation, reverse-use dependency, resembling those more profoundly studied in the SCREENIT assay in rabbit heart described below). The species plays an important role in drug-induced prolongation of APD and incidence of early afterdepolarizations in the isolated Purkinje fibers and in general, the rabbit constituted the most sensitive and predictive species when electrophysiological responses in Purkinje fibers from rabbits, guinea pigs, dogs, swine, goats and sheep were compared. The dog Purkinje fiber shows a unique (there is no data of their presence in other species, including humans) presence of postsynaptic alpha-2 adrenoceptors. In accordance with the findings with dexmedetomidine, alpha-2 adrenergic stimulation by clonidine and brimonidine results in prolongation of APD in isolated canine Purkinje fibers, apparently through an indirect effect on ITO current. No such alpha-2 mediated electrophysiological effects (or even presence of the receptors) can be identified in the ventricular myocardium. Especially clonidine has been widely used in humans for various indications and it is not known to have any torsadogenic potential. It should also be noted that APD prolongation by alpha-2 agonists in the Purkinje fiber has been shown, in fact, to be protective against ischemic ventricular arrhythmias in rat and canine models by suppressing the beta-adrenergic stimulation-induced delayed afterdepolarizations and sustained triggered activity (Cai JJ et al., 2002,Samson RA et al., 1995).

The cardiac electrophysiological effects of dexmedetomidine and its H-3 metabolite have been studied more thoroughly in the isolated Langendorff perfused female rabbit heart model (SCREENIT). The model has been extensively validated with a large number of compounds and shown to reliably separate torsadogenic/non-torsadogenic agents (Hondeghem L, 2008, Valentin JP et al., 2004). Dexmedetomidine as well as H-3, studied up to 3 μM concentrations, had no significant effects in this model. Most importantly, there were no signs of proarrhythmia nor repolarization disturbance such as

early afterdepolarizations and TdP. It can thus be concluded that on the basis of the results of this well done study in a highly predictable model dexmedetomidine is not expected to promote arrhythmias related to effects on conduction or repolarisation.

As set in the ICHS7B guideline, in vivo assays are also needed to establish an integrated cardiovascular risk assessment of a compound. Effects of dexmedetomidine on QT interval have been studied in conscious dogs using standard telemetry methodology and in anaesthetized guinea pigs. When given to conscious dogs as a continuous s.c. infusion of 10 µg/kg/h for 7 days, a very marked decrease in heart rate was seen. This was, as expected, accompanied with a marked increase in QT interval duration. When corrected for heart rate, QTcBazett and QTcFridericia were essentially unchanged but when QT was corrected using Sarma's method, a clear increase was seen. On these very low heart rates the Bazett's and Fridericia's formulas probably undercorrect the QT values while the Sarma's type methods may be more appropriate (Champeroux P et al., 2009). It is, however, possible that at the very low levels of heart rate induced by dexmedetomidine the normal QT/RR relationship is not relevant resulting in an overestimation of QT values even with a Sarma-type individual correction method. Even more importantly, it has recently become clear that besides heart rate, the body temperature has a significant influence on ventricular repolarisation so that a decrease in body temperature is accompanied by an increase in QT interval duration. Van der Linde et al (Van der Linde H et al., 2008) showed convincingly that the measured QT interval should be corrected also for the changes in body temperature to avoid misleading interpretation of drug-induced effects on QTc.
During the 7-day s.c. infusion in dogs, dexmedetomidine induced also a marked decrease in body temperature. Body temperature decrease and apparent dexmedetomidine induced QTSarma prolongation were, indeed, strongly correlated suggesting that the effect of dexmedetomidine may be due to hypothermia. This was proved convincingly in a follow-up study where dogs were infused with dexmedetomidine either with or without body temperature control. QTSarma increased only in hypothermic animals.
Overall the company concluded that dexmedetomidine and its major human metabolites are devoid of any significant hERG blocking activity. Moderate APD prolongation is evident in the dog Purkinje fiber assay at supratherapeutic dexmedetomidine concentrations but in the isolated rabbit heart preparation (SCREENIT) dexmedetomidine and its H-3 metabolite do not have any electrophysiological effects (e.g. prolongation of APD, triangulation, instability, reverse-use dependency, early afterdeporazations), linked to torsadogenicity. Dexmedetomidine showed apparent prolongation of QTSarma in dogs in vivo but the Expert agrees that the effect is most likely an indirect physiological effect via hypothermia and dexmedetomidine thus does not carry any proarrhythmic electrophysiological effects. Therapeutic hypothermia is widely used in ICU for preventing neurologic injury and mild to moderate hypothermia (≥ 30○C), despite of an increase in QTc, is not known to increase risk for clinically significant arrhythmias (Polderman K et al., 2009). Therefore on the basis of the nonclinical studies done, it is unlikely that dexmedetomidine has any torsadogenic potential in humans at the therapeutic dose range and well above.

The effects of dexmedetomidine and its available main human metabolites (the oxidation product H-3 and the N-glucuronides G-Dex-1 and 2) on cloned human ether-à-go-go related gene (hERG) channels were studied in HEK cells. Dexmedetomidine and the metabolites blocked the hERG current only at very high concentrations (half maximal inhibitory concentration [IC50] values for all compounds were ≥ 10-30 µM). Dexmedetomidine and the H-3 metabolite did not show significant binding affinity (at a concentration of 1 µM) on L-Ca2+, K+ATP, K+V, Na+V or chloride channels in a receptor screening assay. The effects of dexmedetomidine on cardiac action potential were assessed in a screening study using isolated canine Purkinje fibre. Dexmedetomidine at a concentration of 0.01 µM had no effect on action potential parameters. At concentrations of 0.1 and 1 µM, a slight, dose-dependent increase in action potential duration (APD) was observed. In contrast 10 µM dexmedetomidine induced a decrease in APD which was associated with decrease in the maximal rate of depolarisation, suggesting possible inhibition of calcium and/or sodium currents at this highly supratherapeutic concentration. Early or delayed afterdepolarisations were not observed at any dexmedetomidine concentration. Using a TDPscreenTM categorisation (Champeroux P et al., 2005)

developed by the laboratory performing the assay (CERB), dexmedetomidine was assessed to belong to compounds which have a very low risk for torsadogenesis.

The cardiac electrophysiological effects of dexmedetomidine and the H-3 metabolite were studied in isolated Langendorff perfused female rabbit hearts using the SCREENIT-model. The method measures: automaticity and escape cycle length, threshold stimulation current, coronary perfusion rate, ectopic activity, left ventricular septal and epicardial monophasic APD at 30, 60 and 90% repolarisation, conduction time, triangulation (APD90-APD30), reverse use-dependence, instability (beat-to-beat variability in APD), and dispersion of repolarisation (beat-to-beat variability between septal and epicardial APD60). The development and number of early afterdepolarisations and torsade de pointes (TdP) were detected using an automated computer algorithm. Dexmedetomidine and the H-3 metabolite had no significant effect upon any of the parameters measured, over the full range of concentrations studied. There was no indication of proarrhythmia or repolarisation disturbance, such as early afterdepolarisations and TdP. The effect of dexmedetomidine on QT interval was studied in conscious dogs using standard telemetry. A single-dose study with veterinary bolus doses (500 µg/m2 i.m. and 375 µg/m2 i.v., corresponding to about 23 and 17 µg/kg respectively, and achieving peak plasma dexmedetomidine concentrations of 6-10 ng/ml). Highly significant dexmedetomidine-induced bradycardia was apparent and QT-intervals were increased. However when corrected for the decreased heart rate, the QTcBazett and QTcFridericia values were actually slightly shortened while QTSarma remained unchanged.

In another in vivo cardiovascular safety pharmacology study dexmedetomidine was administered to conscious dogs as a continuous s.c. infusion of 10 µg/kg/h for 7 days (achieving plasma concentrations of about 3 ng/ml). Animals experienced deep/moderate sedation, marked bradycardia, an increase in blood pressure and marked hypothermia. No effects were seen on QTc when corrected for the lowered heart rate with Fridericia formula. QTcBazett was slightly decreased whereas QTSarma was markedly prolonged. The marked bradycardia complicated the use of the correction formulas and interpretation of the results. In addition, it seemed that the increase in the duration of ventricular repolarisation (QTSarma) occurred in parallel /with concomitant hypothermia. Electrocardiogram (ECG; measuring QRS, QT and RR intervals), heart rate, blood pressure and body temperature were analysed at 5 minute intervals. In dogs without a heating blanket a temperature decrease of up to -4 degrees C was seen, as in the previous 7-day infusion study; in animals with a heating blanket body temperature was maintained at pre-dose levels or slightly above. The animals were equally sedated in both groups. Heart rate was slightly lower in the hypothermic animals. The QTSarma increased in the hypothermic animals but no such an effect was seen if the body temperature was normalised. The effect of dexmedetomidine on QTSarma is, therefore, likely to be due to hypothermia and not linked to torsadogenic electrophysiological changes. Van der Linde et al (Van der Linde H et al., 2008) have recently studied the influence of drug-induced body temperature changes on ventricular repolarisation and came to the conclusion that the measured QT interval should be corrected also for changes in body temperature, to avoid misleading interpretation of QTc effects. In anaesthetised guinea pigs, cumulative i.v. infusion of dexmedetomidine (9, 27 and 90 µg/kg/h at 20 min intervals, achieving mean plasma concentrations of 1.5, 3.7 and 10.4 ng/ml respectively) did not induce any effects on the duration of ventricular repolarisation; when cisapride was used as a positive control it showed a typical QT prolonging effect

Reviewer conclusions: *In the dog Purkinje fiber assay (TDPscreenTM)), dexmedetomidine (1 µM) induced a slight increase in APD. The company categorizes this effect as similair to compounds which cause TdP only in very rare cases.* The company provides a comparison with other *compounds of a similar ranking specifically risperidone, ondansetron and fluoxetine. The company stated (at the time) that those compounds have not shown any proarrhythmic problems despite their wide clinical use. Today, all these products mentioned have QT interval prolongation as a labelled effect in their respective SPCs. From the preclinical data submitted, Dexdor appears to cause marked hypothermia which could provide a plausible mechanism of action. In the SPC of Dexdor, this is mentioned in relation to paediatrics but not for adults.*

4.8 A single case of hypothermic bradycardia in a neonate has been reported in the literature.

5.1 New-born infants may be particularly sensitive to the bradycardic effects of Dexdor in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.

In a study by Khan and colleagues, a 4 patient case series is presented which demonstrates that hypothermia carries potential for fibrillation They conclude that a hypothermic myocardium is intrinsically prone to arrhythmias and that this can be worsened with the addition of drugs that *can prolong the QTc.* (Khan et al, 2010)*. The hypothermic effect of dexmedetomidine could be considered as a contributing factor to QT interval prolongation.*

Summary of company clinical data

In common with other alpha-2 agonists, dexmedetomidine reduces HR. It results in adverse events of bradycardia as well as prolonged PR and QT interval on the 12-lead electrocardiogram (ECG). In the ICU most patients have elevated HR, whether related to pain, sepsis or many other possible causes and the effect of dexmedetomidine is commonly to reduce HR towards normal values. Although values below the normal range are common, only 4% of dexmedetomidine patients had bradycardia sufficiently severe to require treatment (normally anticholinergics) in comparator controlled double-blind ICU studies. The episodes of sinus pause or arrest seen in healthy volunteers and non-ICU studies are less apparent in ICU patients, probably reflecting high sympathetic tone. The use of continuous monitoring in an ICU setting described in the SPC along with anticholinergic treatment for symptomatic or severe cases should result in bradycardia rarely presenting a clinical problem. However, great care should be taken in patients with pre-existing low HR or heart block, unless paced, and dexmedetomidine should generally be avoided in such patients. It is notable that the incidence of atrial fibrillation is modestly reduced on dexmedetomidine which might reflect the effect on HR.
Asystole was reported in a patient with myasthenia gravis on oral pyridostigmine following sternal retraction during thoracic surgery under dexmedetomidine which was successfully treated with open cardiac massage and epinephrine.
Asystole leading to death was reported in a 76 year old female patient given dexmedetomidine for removal of an infected pacemaker (originally inserted for symptomatic bradycardia). The event occurred during dexmedetomidine loading dose and ECG showed pacing spikes without capture.

Repeated bradycardia leading to brief asystole was also reported in an 18 year old double-lung transplant recipient during periods of coughing and hypoxia. The events were self-limiting without specific treatment. This patient had already had frequent episodes of bradycardia associated with hypoxia during coughing fits prior to receiving dexmedetomidine. These cases confirm that care should be taken in patients already pre-disposed to bradycardia.

Severe hypotension leading to death was reported in a 50 year old male patient sedated with dexmedetomidine for ablation of paroxysmal atrial fibrillation. During sedation the patient became agitated and sat up abruptly leading to severe hypotension. The hypotension was relieved by pericardiocentesis of 100 ml blood however he rapidly deteriorated with global left ventricular dysfunction. Although haemodynamic function was eventually improved he died due to anoxic brain injury. At autopsy there was diffuse myocardial necrosis and perforation of the left atrium. The initial hypotension was clearly caused by inadvertent perforation of the atrium with consequent haemopericardium, however the dexmedetomidine might have affected the patient's inability to recover from that insult.

An 18 year old patient with transverse myelitis developed severe hypertension and bradycardia during a loading dose of 2 ug/kg of dexmedetomidine over 10 minutes which resolved within a few minutes. In this case the dose of dexmedetomidine was very high but it may indicate along with the case of the 50 year old male that haemodynamic responses to dexmedetomidine might be exaggerated in patients with impaired peripheral autonomic activity.

A thorough QT study was not done for this dossier. The company justifies this because in volunteers it is not sufficiently safe to maintain supra-therapeutic concentrations of dexmedetomidine as proposed in the ICH E14 guidance and a very different physiological status would somewhat restrict interpretation of such a study even if performed. In ICU patients (where consent is commonly given by legal representative) the study design would be contrary to standard clinical practice and unlikely to be ethical. However, the non-clinical data suggest that dexmedetomidine does not alter cardiac repolarisation based on hERG channel work and in temperature maintained dogs. QTc was thus assessed by repeated measurements analysed according to the International Conference on Harmonisation (ICH) E14 guidance. In addition, it is very relevant that dexmedetomidine is intended for use in the ICU where patients have continuous ECG monitoring and have intense care from personnel experienced in detecting and managing arrhythmias.

Reviewer conclusions: *Cardiovascular events due to low BP or HR are expected and thus caution is advised for patients who have a predisposition or in patients who experience this at the start of dexmedetomidine treatment. Monitoring both parameters closely and being ready to treat significant decompensation in those patients where it occurs is the main cardiovascular harm prevention strategy outlined by the company in the SmPC which states that care should clearly be exercised, and suitable monitoring in place, when co-administering dexmedetomidine with other drugs that may reduce BP and HR as there is a possibility of additive effects.*

Scientific literature

Kim et al (2016) Effect of Dexmedetomidine on Heart Rate-Corrected QT and Tpeak-Tend Intervals During Robot-Assisted Laparoscopic Prostatectomy With Steep Trendelenburg Position: A Prospective, Randomized, Double-Blinded, Controlled Study.

Intraperitoneal insufflation of carbon dioxide may affect the sympathetic activity that leads to changes in ventricular repolarization. This in turn can result in changes of heart rate-corrected QT (QTc) interval and Tpeak-Tend (Tp-e) interval. Dexmedetomidine is a highly selective α2-receptor agonist and has potential antiarrhythmic properties. This prospective, randomized, double-blinded, controlled study evaluated the effects of dexmedetomidine administration on QTc and Tp-e intervals during robot-assisted laparoscopic prostatectomy with steep Trendelenburg position.Fifty patients scheduled for robot-assisted laparoscopic prostatectomy randomly received either a continuous infusion of dexmedetomidine at a rate of 0.3 μg/kg/hour, from anesthetic induction until the end of the Trendelenburg position (dexmedetomidine group; n=25), or the same volume of normal saline (control group; n=25). Anesthesia was maintained with sevoflurane and remifentanil. The primary and secondary goals were to evaluate the effect of dexmedetomidine on the QTc and Tp-e interval changes. Mean arterial pressure, heart rate, end-tidal CO2, and end-tidal sevoflurane concentrations were assessed as well. Forty-seven patients (94%) completed the study. Dexmedetomidine significantly attenuated QTc interval prolongation and reduced the Tp-e interval, even though the baseline values of the QTc and Tp-e intervals were similar between the 2 groups (PGroup×Time=0.001 and 0.014, respectively). Twenty-two patients (96%) in the control group and 13 (54%) in the dexmedetomidine group had QTc interval prolongation of >20 ms from the baseline value during surgery (P=0.001). The maximum QTc interval prolongation from the baseline value during surgery was 46±21 ms in the control group and 24±21 ms in the dexmedetomidine group (mean±SD, P=0.001). Mean arterial pressure and heart rate were comparable between the groups. Continuous infusion of dexmedetomidine at a rate of 0.3 μg/kg/hour significantly attenuated the QTc interval prolongation induced by CO2 pneumoperitoneum with steep Trendelenburg position. Furthermore, dexmedetomidine reduced the Tp-e interval. Thus, dexmedetomidine administration may be effective for patients who are susceptible to the development of ventricular arrhythmia during robot-assisted laparoscopic prostatectomy. (Kim et al, 2016)

Reviewer conclusions: *This study provides reassurance on the effects of dexmedoetmidine and suggests that it may have a QT attenuation effect and is not proarrythmic.*

Cho (2016) Effects of Dexmedetomidine on Changes in Heart Rate Variability and Hemodynamics During Tracheal Intubation.

Sympathetic hyperactivation during tracheal intubation prolongs the QT interval and increases the risk of arrhythmias. We investigated if dexmedetomidine pretreatment affected autonomic nervous system balance and QT intervals during intubation. Sixty-six patients were randomized to receive 1.0 μg/kg fentanyl (group F, n = 22), 0.5 μg/kg dexmedetomidine (group D0.5, n = 22), or 1.0 μg/kg dexmedetomidine (group D1.0, n = 22) before induction. Autonomic nervous system balance was assessed by the ratio of low-frequency/high-frequency (LF/HF) power for heart rate variability at baseline (T0), before intubation (T1), and after intubation (T2). QT intervals were corrected by the Bazett's formula (QTc) and compared at baseline, before intubation, and 1, 2, and 3 minutes after intubation. The LF/HF ratio was higher after intubation compared with that at T0 in group F ($P < 0.001$). There were no significant changes in groups D0.5 and D1.0. The LF/HF ratio was significantly higher in group F compared with those in groups D0.5 and D1.0 after intubation (7.9 vs. 2.1 and 2.5; $P < 0.001$). The heart rate was increased for 3 minutes after intubation in group F, whereas only for 1 minute after intubation in groups D0.5 and D1.0, compared with that at baseline. More patients in group F had QTc greater than 440 ms compared with that in group D0.5 or D1.0 (8 vs. 1 and 2; $P = 0.005$) at 1 minute after intubation. In contrast to 1.0 μg/kg fentanyl, pretreatment with 0.5 or 1.0 μg/kg dexmedetomidine suppressed sympathetic hyperactivity and attenuated QTc prolongation during intubation.

Reviewer conclusions: *This study provides reassurance on the effects of dexmedoetmidine and suggests that it may have a QT attenuation effect and is not proarrythmic.*

Gorges et al (2015) Changes in QTc associated with a rapid bolus dose of dexmedetomidine in patients receiving TIVA: a retrospective study.

Background: Clinical indications for the perioperative use of dexmedetomidine in pediatric anesthesia are accumulating. However, in 2013, dexmedetomidine was added to the list of medications with possible risk of prolonging the QT interval and/or inducing Torsades de Pointes. Unfortunately, current evidence for dexmedetomidine-induced QT prolongation is sparse and somewhat contradictory. The purpose of this study was to evaluate temporal changes in corrected QT interval (QTc) after a rapid bolus administration of dexmedetomidine under total intravenous anesthesia (TIVA) with a standardized propofol and remifentanil administration. Method: Electrocardiography (ECG) and corresponding trend data were extracted from automated electronic data capture of physiological monitoring. Ten-second epochs of ECG data were extracted in 1-min intervals for 12 min, starting 1 min before dexmedetomidine bolus administration, and ending 10 min after. QT intervals were extracted using an automated routine in MATLAB, and corrected for heart rate (HR) using Bazett's (QTcB) and Fridericia's formulas (QTcF). QTcB and QTcF were compared using Wilcoxon signed-rank test between baseline measurements and the subsequent four interval values. Results: Data from 21 subjects (17 male) with median (range) age 7.1 (5.4-9.5) yr, weight 23.6 (16.2-36.7) kg, and height 121 (103-140) cm were analyzed. Bolus administration of dexmedetomidine reduced HR in all subjects (median 22%), and caused transient reduction of QT interval, with its peak at 1-min postbolus administration: QTcB (median reduction 30.7 ms, $P < 0.001$) or QTcF (median reduction 15.4 ms, $P = 0.001$); QT shortening became statistically insignificant 4 min following dexmedetomidine bolus administration for QTcB and 2 min for QTcF. Conclusion: In this study, a rapid bolus of dexmedetomidine transiently shortened corrected QT intervals. However, these effects are confounded by dexmedetomidine-induced bradycardia. These findings should be confirmed in pediatric studies without concomitant TIVA administration and with optimized correction of baseline HR. (Gorges et al, 2015)

Reviewer conclusions: *This study provides reassurance on the effects of dexmedoetmidine and suggests that it may have a QT attenuation effect and is not proarrythmic.*

Burns & Greene (2014) Long QT syndrome unmasked by dexmedetomidine: a case report.

Dexmedetomidine is a selective alpha-2 adrenergic agonist that is used frequently for short-term sedation in children. It has been noted to cause hypertension, hypotension, bradycardia, and sinus pauses; however, QTc prolongation has not been reported with dexmedetomidine administration. We describe a case of marked QT prolongation with use of dexmedetomidine in a pediatric critical care setting. Clinicians should be vigilant about potential QT prolongation in patients on dexmedetomidine, particularly in those receiving multiple other medications. (Burns and Greene, 2014)

Reviewer conclusions: *Case reviewed elsewere; US-EMA-20150203-tanvievhp-125057799 (see Case number 8, post marketing section below)*

Shields (2008) Heart block and prolonged Q-Tc interval following muscle relaxant reversal: a case report.

Heart block and Q-Tc interval prolongation have been reported with several agents used in anesthesia, and the US Food and Drug Administration mandates evaluation of the Q-T interval with new drugs. Drug-induced Q-T interval prolongation may precipitate life-threatening arrhythmias, is considered a precursor for torsades de pointes, and may predict cardiovascular complications. In the patient described in this article, heart block occurred and the Q-Tc interval became prolonged after muscle relaxant reversal with neostigmine; both were considered to be related to the combination of agents used in the case, as well as to other predisposing factors such as morbid obesity. The agents used that affected cardiac conduction were neostigmine, desflurane, droperidol, dolasetron, and dexmedetomidine. Although the heart block was resolved after 2 doses of atropine, prolonged P-R and Q-Tc intervals persisted into the immediate postoperative period but returned to baseline within 4 hours. Clinical implications of this report include increasing awareness of the multitude of factors affecting Q-T interval prolongation during anesthesia. (Shields, 2008)

Reviewer conclusions: *Case reviewed elsewere; US-EMA-20110307-slalp-141536773 (see Case number 5 post marketing section below)*

Post-marketing pharmacovigilance data review:

Case 1: 46 years-old male patient with stroke and hypertensive emergency experience QT interval prolongation while undergoing treatment in the ICU. The following products were considered as suspect: Dexmedetomidine Fentanyl, Midazolam, Quetiapine. The patient did not have liver failure and suffered delirium which was treated with Dronabinol. The event is unexpected as per the US PI of Midazolam; and expected as per the US PI of Quetiapine. US-SUN PHARMACEUTICAL INDUSTRIES LTD-2015US-106776

Reviewer comment:

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 2: 62 years-old female patient with the following events Bradycardia and Electrocardiogram QT prolonged. Patient's medical history included: Smoker (ongoing), alcoholic, hypertension, chronic kidney disease, acute necrotizing pancreatitis, acute respiratory distress syndrome and shock. Following products were considered as suspect: Quetiapine, Dexmedetomidine. Dronabinol rectally for 5 mg bid for 48 hrs was given as treatment for delirium. The events are expected as per the US PI of Quetiapine. Medical reviewer assessed the events to be possibly related to company suspect drugs. US-SUN PHARMACEUTICAL INDUSTRIES LTD-2015US-106829

Reviewer comment:

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: reports on Electrocardiogram QT prolonged coincident with dexmedetomidine hydrochloride (Precedex injection) therapy. On 8 Mar 2007, the patient underwent surgery for aortic valve insufficiency. Precedex injection therapy was administered for sedation. On 9 Mar 2007, the patient experienced electrocardiogram QTprolonged. The patient was treated with an unreported dose of lidocaine and the patient was recovering. The reporter believed the event was possibly related to the Precedex injection therapy. JP-Hospira-07h-087-0312585-00

Reviewer comment:

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0

Dechallenge	C3	Alternate	S1
Result	I3	Probable	

Case 4: an 8-month-old girl received dexmedetomidine (DEX) (0.6 mcg/kg/min then increased to 0.66 mcg/kg/min, intravenous infusion) for sedation on an unknown date. The patient had been in hospital since birth for a number of problems. Necrotizing enterocolitis (NEC) at birth led to ileal stenosis, which required multiple surgeries over a several-month period. At the age of 17 weeks, she had gastroesophageal reflux. Treatment with lansoprazole [4 mg twice daily (2 mg/kg/day), oral] and metoclopramide was initiated. The oral metoclopramide dose varied from 0.8 to 1 mg three or four times daily (0.6-0.8 mg/kg/day) up to the age of 29 weeks. At that point, because the child's reflux persisted, the medical team changed the treatment. Pantoprazole [4.5 mg twice daily (1.9 mg/kg/d), intravenous] and cisapride [0.9 mg four times daily (0.8 mg/kg/d), oral] were then administered. Concomitant medications included fentanyl (10 - 20 mcg, intravenous) prior to suction, rocuronium (6 mg as required, intravenous) if patient fights ventilator, midazolam (dose not reported, intravenous infusion), acetaminophen (85 mg 4 to 6 times daily as required, PO/IR), benztropine (0.12 mg twice daily, intravenous), diphenhydramine (5.7 to 6 mg 4 times daily, intravenous), furosemide (6 mg 3 or 4 times daily as required, intravenous), hydromorphone (dose not reported, intravenous infusion), ursodeoxycholic acid (60 mg 3 times daily, oral), ketamine (dose note reported, intravenous infusion) for unknown indications and omeprazole (6 mg twice daily, oral) for gastroesphageal reflux. The patient was born at 28 6/7 weeks gestation. At 32 weeks of age, the little girl underwent her third operation, during which the ileostomy was closed and a gastrostomy was created. Pantoprazole and cisapride were stopped. After the operation, the patient was transferred to the intensive care unit, where she was intubated. The gastrointestinal problem persisted. Metoclopramide was introduced again, this time intravenously. Since she had tracheomalacia, extubation promised to be difficult. To avoid injury to the trachea, which was rather narrow and inflamed, adequate sedation was sought. Unfortunately, the initial medication (dose and route of administration not reported) proved inadequate, so it was decided to introduce dexmedetomidine in order to achieve optimal sedation. Thus, DEX was administered for 4 days (D-4 to D-1), with no satisfactory improvement in sedation (cumulative dose received as of Day -1: 336.50 mcg, or 46 mcg/kg). On Day 0 (D0), the patient's electrocardiogram (ECG) showed QT interval prolongation (520/591 ms [milliseconds] - QT/QTc). She was then 8 months old and weighed 7.3 kg. The values remained high on D1 (470/555 ms) and D3 (394/525 ms). It should be noted that she was also treated for agitation with haloperidol for six days (cumulative dose as of D0: 5.6 mg, or 0.76 mg/kg). Since haloperidol is known for its potential to increase the QT interval, it was stopped on Day 0, as soon as QT interval prolongation occurred. Despite the fact that the haloperidol had been stopped, no improvement was seen on the ECG in the days that followed. On Day 3, given that the QT interval prolongation persisted, it was decided to stop the metoclopramide. The ECG normalized on Day 5. It should be noted that she had had an ECG in the past (day -50), before treatment with cisapride was started. At that time, the ECG was normal. During this episode, hypokalemia and minor bradycardia were noted. No hypermagnesemia was noted. The author stated, “Lastly, it is important to note that there was the potential for several drug interactions. First, metoclopramide is an average cytochrome P450 2D6 substrate, while, in vitro, DEX (dexmedetomidine) is a strong potential inhibitor of this cytochrome. Given these interactions, we are likely to observe an increase in metoclopramide concentrations and in the risk of adverse effects associated with this drug.” The author also stated, “Here is a case of QT prolongation in a polymedicated child in a health-care institution.” The author also stated, “Using the Naranjo algorithm to assess causality, we obtained a score of 5 for metoclopramide, as well as for haloperidol, which indicates that these drugs were probably involved in this occurrence of QT interval prolongation." The author also stated, “In addition, bradycardia causes slower repolarization, which increases the risk of QT interval prolongation. Bradycardia is not foreign to the addition of dexmedetomidine, which is known to cause this cardiac effect in 5 to 14% of patients.” The author further stated, "Thus, DEX was administered for 4 days. She was then 8 months old and weighed 7.3 kg." Metoclopramide, haloperidol, and chloral hydrate were also considered suspects. Hypokalemia and polypharmacy were considered contributing factors. CA-HOSPIRA-930717

Reviewer comment: *Outcome using French tool is Uncertain. Other alternate explanations could be metoclopramide and haloperidol.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 5: 41-year-old female patient, who developed a life-threatening second degree heart block and prolonged QTc interval during a gastric restrictive procedure with short-limb Roux-en-Y gastroenterostomym, following the use of dolasetron and droperidol for prevention of post operative nausea and vomiting, neostigmine administered as reversal of neuromuscular blockade and succinylocholine, dexmedetomidine,fentanyl and desflurane used for anaesthesia. Medical history was significant for smoking and pseudotumor cerebri with shunt placement. Current medications included furosemide for ankle oedema and phentermine for weight loss The patient was admitted to hospital for gastric bypass surgery and preoperative examination revealed the patient's neurological status and laboratory findings were unremarkable. Her serum potassium levels were 4.4mEq/L. An electrocardiogram showed normal sinus rhythm, left axis deviation, P-R interval of 0.186 seconds and QT interval of 0.386 seconds. Induction of anaesthesia was accomplished with propfol 150mg, lidocaine 100mg and desflurane. Rapid sequence induction with cricoid pressure was used with succinycholine 200mg. Maintenance of neuromuscular relaxation was achieved with vecuronium (total dose 24mg) and anaesthesia was maintained with desflurane and dexmedetomidine infusion (total dose 324mcg). Fentanyl 5mcg/kg (600mcg) was administered with induction and desflurane was titrated for hemodynamic control and to maintain bispectral monitoring. Intraoperative vital signs were stable. After closure of the fascia, the dexmedetomidine infusion was increased to 0.7mcg/kg per hour and droperidol was administered intravenously for post operative nausea and vomiting. Dolasetron (route and regimen unknown) was also given for the same indication at an unspecified time. Reversal of neuroblockade was accomplished with 0.6 mg of glycopyrrolate and neostigmine 4 mg. The initial signs after administration were stable; however five minutes later, the patient's heart rhythm suddenly converted into second degree heart block with a ventricular rate of 31 beats per minute and a prolonged P-R interval (0.24 seconds). Vital signs included a blood pressure of 82/42 and an oxygen saturation of 92%. This rhythm persisted for four minutes and twenty four seconds, during which time atropine 0.4 mg was administered. The rhythm subsequently returned to normal and blood pressure increased to 101/65 mmHg. The dexmedetomidine infusion and nitrous oxide were immediately discontinued and the fraction of inspired oxygen (FI02) was increased to 1.0 and desflurane was reinstituted. Closure of the skin was ensued and preparations were made for emergence and extubation of the patient. Two minutes and thirty six seconds after the patient's heart rate returned to normal rhythm, second degree heart block reoccurred with an atrial rate of 74 beats per minute (bpm) and ventricular response of 37 bpm. Vital signs included a blood pressure of 106/54 mmHg and oxyhaemoglobin saturation of 95%. The P-R interval was 0.24. Treatment with atropine 0.4mg was initiated and within 72 seconds the rhythm reverted to sinus rhythm. Hemodynamic parameters remained unchanged until the procedure was complete, at which time desflurane was discontinued. A 12-lead ECG performed four hours after dexmedetomindine was discontinued revealed a P-R interval of 0.177, QT interval 0.312 and QTc of 0.414. On emergence, the patient's neurological signs were intact and she had an adequate respiratory effort and was subsequently extubated. No cardiovascular symptoms were noted and post operative blood pressure was 140/70 mmHg, heart rate 74 bpm, and respiratory rate of 16 breaths per minute. An ECG showed a QT interval of 0.403 and QTc of 0.441 seconds. The patient remained mildly sedated and no additional pain medications were required until discharge from post anaesthesia unit. Four hours post emergence, the rate-corrected QT interval (QTc) was reported as being within normal limits. The reporter concluded that due to the refractory nature of the QTc interval prolongation, the heart rhythm and conduction changes were related not only to neostigmine but also to the concomitant use of longer lasting agents, dolasetron, droperidol and dexmedetomidine. Fentanyl was considered an additional suspect medication by the author, as it may

have resulted in an addictive effect on the Q-T interval and co-suspect desflurane was commented to be associated with a higher degree of QT interval prolongation. Other Relevant History text: Pseudo-tumour cerebri with shunt placement, and use of phentermine for weight loss. Ankle oedema in both legs. Preoperative cardiovascular examination demonstrated regular rate and rhythm, with no rubs or murmurs. An ECG revealed normal sinus rhythm, with left axis deviation, a P-R interval of 0.186 sec, and a Q-T interval of 0.386 sec. US-EMA-20110307-slalp-141536773

Reviewer comment: *Outcome using French tool is Uncertain. Phentermine provides a more likely explanation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 6: 05.12.2013 Case of severe brain injury and high intracranial pressure due to strong sedation occured. 3.12.2013 It was intended to lighten sedation and give up long-lasting midazolam infusion for dexmedetomidine infusion. Before dex start of the infusion, a prolonged QT interval> 500 msec was observed. Four hours after the start of the dex infusion, the QT interval had prolonged to > 700 ms, AV conduction abnormalities (intermittent totaaliblokki), good ventricular, (monitor resembled torsades de pointes, tachycardia). Dex infusion was discontinued. Sedation was maintained with thiopental bolus. Arrhythmias were treated with bolus of lidocaine and magnesium sulphate. High dose bolus noradrenaline was given in order to maintain blood pressure levels FI-FIMEA-20132014.

Reviewer comment: *QT prolongation started before the administration of the drug, but may have worsened with drug administration.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatable	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 7: A healthcare professional reported that a 26-year-old male patient (height: 178 cm and weight: 71 kg) received Precedex (Dexmedetomidine Hydrochloride), possible lot numbers 27322DK and 21400DD; dose initially started at 0.4 mcg/kg/hr then titrated at 0.8 mcg/kg/hr, IV) for sedation on 27-Jan-2014. The patient had no history of allergies. On 27-Jan-2014, the patient received Dexmedetomidine Hydrochloride mixed with Baxter Normal saline (50 cc, frequency unknown, IV) and Quetiapine (25 mg, frequency unknown, oral) for an unknown indication. At 10:30, about 5 minutes later, prolonged QT and T wave inversion were noted on telemetry. Laboratory tests and treatment were unknown. It was stated by the reporter that the dose was decreased to 0.2 mcg/kg/hr and then discontinued. Duration of Dexmedetomidine Hydrochloride was reported as 30-45 minutes. It was reported that T wave inversion was resolved and QT prolongation was not seen on the normal EKG. On the same day, at 11:15, the patient recovered from the event. The reporter considered the events probably related to Dexmedetomidin Hydrochloride. Alternative etiology/contributing factor was reported as "Patient also received Quetiapine 25 mg orally, 30 minutes prior noticing EKG changes." Overall case causality: Probable. The patient had no history of allergies. Tobacco use, alcohol use and medical history were unknown. Outcome by reporter: recovered/resolved Medical

Evaluation Comment: Prolonged QT and T wave inversion are assessed as unexpected according to current Dexdor EU SPC. US-Orion Corporation ORION PHARMA-DEX 2014-0041

Reviewer comment: *The adverse event started before the drug was administered. Quetiapine provides a more likely explanation for worsening of QT interval prolongation. Causality is uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 8: this case is about unmasking of long QT syndrome by dexmedetomidine. This report refers to a 22-month-old male patient with a history of repaired left-sided congenital diaphragmatic hernia, left lung hypoplasia, and severe asthma who was admitted to the pediatric intensive care unit with complicated pneumonia. His medical history is significant for persistent pulmonary hypertension of the newborn related to congenital diaphragmatic hernia. In the neonatal period, he required extracorporeal membrane oxygenation (ECMO) support. He has severe asthma and has been hospitalized multiple times for pneumonia. He also has a distant history of supraventricular tachycardia (without manifest pre-excitation) and was treated with digoxin for several months after birth, with no recurrence of arrhythmia. Given his history of neonatal supraventricular tachycardia, 14 previous electrocardiograms were available for review. The most recent electrocardiogram 15 months prior to this incident had a QTc interval of 427 milliseconds. At that time, the patient was receiving albuterol, digoxin, hydrochlorothiazide-spironolactone, ipratropium, metoclopramide, prednisolone, and ranitidine. All other prior QTc intervals were normal (356-442 milliseconds) except on one electrocardiogram performed on day of life 3 while on ECMO that had a prolonged QTc interval of 490 milliseconds. The patient's mother has had several episodes of syncope. On admission to the pediatric intensive care unit, he was placed on supplemental oxygen and underwent thoracostomy for a significant left pleural effusion. Two days after admission, he developed respiratory failure and required intubation. After intubation till administration of dexamedetomidine, the patient was on budesonide, hydrochlorothiazide-spironolactone, ipratropium, lansoprazole, fentanyl, rocuronium, vecuronium, midazolam, morphine, vancomycin, ceftriaxone, furosemide, acetaminophen, and docusate. He initially received morphine and midazolam infusions for sedation; however, after 66 hours, he was transitioned to morphine (0.12 mg/ kg/h) and dexmedetomidine infusions (1 mcg/kg loading dose followed by a titrated infusion rate of 0.3-0.7 mcg/kg/h) in preparation for extubation. Four hours after starting the dexmedetomidine infusion, he developed sinus bradycardia but had no significant fluctuations in blood pressure. Eight hours later, he was noted to have giant T waves on the cardiac monitor. An electrocardiogram revealed profound QTc prolongation (700 milliseconds) with T-wave alternans, a precursor to torsades de pointes. At the time of this marked change in his electrocardiogram, he had not received an albuterol treatment for 3 days, and he was not receiving any other medications known to prolong the QT interval. The patient was on budesonide, hydrochlorothiazide-spironolactone, ipratropium, lansoprazole, morphine, vancomycin, ceftriaxone, furosemide, methylprednisolone, acetaminophen, docusate, glycerin, in time interval from dexmedetomidine to QTc prolongation (20 hours). Laboratory analysis at the time was notable for mild hypocalcemia, therefore calcium gluconate was given for repletion. (Capillary blood gas: pH 7.55, pCO2 45 mm Hg, pO2 59 mm Hg, base excess 15; ionized calcium 1.01 mmol/L, magnesium 1.8 mg/dL, and potassium 3.7 mmol/L). Trends in blood gases and electrolytes revealed a transient respiratory acidosis 21 to 26 hours prior to the event. The lowest potassium level was 3.3 mmol/L 14 hours earlier. The dexmedetomidine infusion was discontinued, and he was extubated without difficulty 10 hours later. After discontinuation to dexmedetomidine, the patient was on budesonide, hydrochlorothiazide-spironolactone, ipratropium, lansoprazole, midazolam, morphine, ceftriaxone, furosemide, methylprednisolone, acetaminophen, docusate, polyethylene glycol and calcium gluconate. The patient was on same regimen till normalization of QTc in addition to magnesium sulfate. Five hours after discontinuation of dexmedetomidine, his QTc interval decreased from 700 milliseconds to

473 milliseconds, and the QTc interval normalized to 439 milliseconds over the next 3 days. He did not develop torsades de pointes or other arrhythmias. A 24-hour Holter monitor placed during this hospitalization after normalization of the QTc interval did not reveal any heart block or significant ectopy but did show variable T-wave morphology at lower heart rates, suggesting abnormal repolarization. Genetic testing was negative for gross deletions or duplications of the 12 genes analyzed for long QT syndrome by targeted comparative genomic hybridization analysis with exon-level resolution. (The 12 genes tested account for at least 75% of long QT syndrome cases.) Clinical suspicion for long QT syndrome type 2 remained quite high; therefore, he was maintained on a potassium-sparing diuretic and started on magnesium supplementation. However, due to a history of severe asthma, the patient was not started on beta-blocker therapy. The author commented that most likely, the additive or synergistic effects of metabolic factors, dexmedetomidine and other concomitant medication use, and genetic predisposition likely led to this patient's dramatic presentation. US-EMA-20150203-tanvievhp-125057799

Reviewer comment: *Challenge and dechallenge information are very suggestive in this case. Mild hypocalcaemia provides an alternative explanation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S1
Result	I3	Probable	

Overall assessment using the Bradford-Hill criteria:

Active substance	BH criterium	Assessment
Dexmedetomidine	Strength of association	4.93 PRR, 8 unique ADR Case reports, 2 of which causality probableand 6 uncertain cases due to confounding factors. 5 articles directly relevant to QT effects were retrieved from the literature. 3 articles point toward an association between demedetomidine and QT interval prolongation and 2 articles which point toward a positive/attenuation role of Dex on the QT interval through QT shortening.
	Biological Plausibility	Dexmedetomidine and the metabolites blocked the hERG current in HEK cells but only at very high concentrations (half maximal inhibitory concentration [IC50] values for all compounds were ≥ 10-30 µM). The effects of dexmedetomidine on cardiac action potential were assessed in a screening study using isolated canine Purkinje fibre and no effect on the AP was seen.
	Biological gradient	Increased QT interval prolongation was not seen with increasing doses of dexmedetomide.
	Experimental evidence and temporality	Of the 8 cases assessed, all had a temporal relationship between the events and the initiation of treatment. Some cases were confounded by other drugs and some occurred in the presence of underlying cardiac conditions or other confounders. 3 studie have been published which show that Dex may have a shortening effect on the QT, and so will be protective when administered with drugs that cause QT interval prolongation. Case reports however suggest that in very rare instances, a paradoxical QT prolongation may occur with administration of the drug. This was seen to be the case in the 22 month old paediatric patient (in association with hypothermia) and in the 41 year old woman with morbid obesity.
	Consistency	There is a level of inconsistency in the overall data package with respect to dexmedietomidine especially from the literature search, with two published cases of clear QT prolongation and 3 (1 US, and 2 South Korean)studies showing that there could be a protective effect of dexmedotimidine on the QT interval.
	Specificity	In preclinical data dexmedetomidine and its metabolites

		were found to bind and block the hERG potassium channel only at massive doses. No effect was seen on the action potential duration.
	Analogy	No anology can be drawn in this case
Overall assessment	***In the Eudravigilance database the association of dexmedotomide with QT prolongation was disproportionally reported for this drug over others. Literature and case review however do not entirely support the relation, and preclinical data does not sufficiently demonstrate a mechanism of action.***	
Benefit Risk Balance	*The benefit risk balance of this product remains positive.*	

Appendix 6:

Glycopyrronium

Glycopyrronium: Seebri Breezhaler 44 micrograms inhalation powder, hard capsules or 200 micrograms/ml Solution for Injection

Mechanism of action: long-acting muscarinic receptor antagonist (anticholinergic) for maintenance bronchodilator treatment of Chronic Obstructive Pulmonary Disease (COPD) in case of inhaler (European Medicines Agency, 2016).

For the injectable form, it is used to

1. Protect against the peripheral muscarinic actions of anticholinesterases such as neostigmine and pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.

2. As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.

3. As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of suxamethonium or due to cardiac vagal reflexes. (Accord Healthcare Limited, 2016)

Date of first EU approval for the active substance: 22/06/2010

Availability in MT: available on the GFL

Currently authorised SmPC wording:

Section	**Wording**
4.3 Contraindications	*Not listed*
4.4 Warnings *(wording is present only for inhaler, not for injectable)*	*Patients with a history of cardiovascular disease Patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc (Fridericia method) was prolonged (>450 ms for males or >470 ms for females) were excluded from the clinical trials, and therefore the experience in these patient groups is limited. Seebri Breezhaler should be used with caution in these patient groups.*
4.5 Interactions	*Not listed*
4.8 List of ADRs	*Not listed*
5.0 Pharmacology	*Not listed*

Number of reports: 3 ICSRs in Eudravigilance database none EU, 3 additional literature cases.

Statistics PRR, CHI^2: 1.819, 1.110

Summary of company preclinical data

In Vitro Cardiovascular Studies

Inhibition of the hERG current was only observed at concentrations significantly higher than the maximum human exposure (Cmax) at the recommended clinical dose. Following administration of 0.01 mg/kg IV (i.e., a 4-fold higher plasma exposure level than that observed clinically based on AUC data), transient effects were seen on heart rate and blood pressure in Beagle dogs. Following an inhaled dose of 0.149 mg/kg (i.e., >100-fold the recommended clinical dose based on allometric scaling using body surface area), transient increases in heart rate and transient decreases in heart rate-corrected QTintervals were observed. However, also PR and P widths were affected at this dose. Moreover, tachycardia was a frequent finding in the dog repeat-dose toxicity studies.

Reviewer conclusions: *Safety pharmacology studies did not reveal any alarming drug effects in the heart at clinically relevant glycopyrronium exposure levels.*

Summary of company clinical data

In a study investigating the safety and tolerability of glycopyrronium (NVA237) in healthy volunteers, Holter monitoring was performed for two i.v. treatments and for inhaled NVA237 without charcoal. The results of a QTc study showed that a single dose of 400 µg of NVA237 (8 times the projected therapeutic dose of 50 µg) had no relevant effect on the corrected QTcF interval. The mean effect and upper limit of the two-sided 90% CI both being below the respective thresholds of 5 ms and 10 ms whereas the positive control, moxifloxacin showed the expected clinical effect on QTcF interval. The slight bradycardic effect observed in other studies was also observed in this study.

Reviewers conclusions: *The results of the QTc study showed that a single dose of 400 µg of NVA237 (8 times the projected therapeutic dose of 50 µg) had no relevant effect on the corrected QTcF interval. The mean effect and upper limit of the two-sided 90% CI both being below the respective thresholds of 5 ms and 10 ms whereas the positive control, moxifloxacin showed the expected clinical effect on QTcF interval. The slight bradycardic effect observed in preclinical studies was also observed in this study. These results provide reassurance.*

Scientific literature

Chiu et al (2016) A case report of QT prolongation with glycopyrronium bromide in a patient with chronic tamoxifen use.

A 78-year-old female with a past medical history significant for breast cancer and moderate COPD presented to Emergency Department with syncope. Nine months prior to admission, she underwent left total mastectomy for invasive ductal carcinoma and was started on Tamoxifen 20 mg daily. Home medications included GB (glycopyrronium bromide) 50 mcg once daily, Salbutamol, calcium and a multi-vitamin. GB was started 3 months prior to her presentation for syncope. The day prior to admission, she received an IV vitamin infusion consisting of a mixture of thiamine, folic acid, multivitamin and magnesium sulfate at a naturopath clinic. Shortly after completion of the IV infusion, she developed emesis and took 2 tablets of dimenhydrinate. The following day, she reported dizziness as she walked across the kitchen and passed out after sitting in a chair. The patient reported no palpitations, chest discomfort, nausea, warm sensation or diaphoresis prior to the syncope event. She was not witnessed to have any seizure like activity and when she regained consciousness, reported immediate awareness of surroundings with no neurological deficits, no tongue biting, bowel or urinary incontinence. There was no previous history of syncope and no family history of sudden cardiac death. Her initial blood pressure in the ambulance was 70/50 mm Hg. Hemodynamics normalized after administration of intravenous fluid and her symptoms resolved. Oxygen saturation was above 97 % and telemetry revealed normal sinus rhythm with a heart rate of 77. Precordial examination was unremarkable with regular normal heart sounds and no murmurs. In the Emergency Department, blood tests including complete blood count (CBC), serum electrolytes (potassium, calcium, magnesium), glucose, creatinine and thyroid stimulating hormone were normal. Electrocardiogram (ECG) showed a corrected QT interval using Fridericia (QTcF) and Bazett's formula (QTcB) of 603 and 631 ms respectively and she was admitted to the cardiology service for further investigation of the etiology for her QT prolongation. Prior to starting Tamoxifen her QTcF and QTcB were 439 and 440 ms respectively, however no ECG was obtained after initiation of Tamoxifen and prior to starting GB. Her last dose of Tamoxifen and GB were the day of admission with both medications discontinued at presentation. An echocardiogram revealed that her left ventricular ejection fraction was >60 % with no valvular or regional wall motion abnormalities. Serial electrocardiograms demonstrated corrected QTcF and QTcB respectively of 603 and 631 ms day 0, 496 and 514 ms day 1, and 446 and 455 ms on day 2 and 442 and 460 ms on day 3. There were no arrhythmias seen on telemetry. Syncope was felt to be secondary to orthostatic changes and she was discharged on day 3 after admission. (Chiu et al, 2016)

Reviewer conclusions: *The temporal relationship with a time to onset of 3 months, is compatible but questionable. A day prior to the event QT prolongation the patient had syncope following administration of an IV infusion and then administration of dimenhydrinate tablets. Magnesium sulphate as contained in the IV infusion can cause intoxication which is manifested by a sharp drop in blood pressure and respiratory paralysis* (FDA Professional Drug Information, 2017) . *However this is usually preceded by sweating and flushing which was not apparent in this patient. Dimenhydrinate can also cause a drop in blood pressure according to its SmPC* (Chelonia Healthcare Limited, 2016). *However, neither magnesium nor dimenhydrinate are expected to cause QT prolongation. Regarding Tamoxifen, the SmPC in section 4.4 states that 'There have been reports in the literature that tamoxifen given at several times the standard dose may be associated with prolongation of the QT interval of an ECG.' However, it is not listed in the section on undesirable effects*

(Generics [UK] Ltd, 2016). *Moreover Thomas and colleagues in 2003, demonstrated that tamoxifen blocked HERG potassium channels with an IC(50) value of 45.3 microM when administered to cloned HERG potassium channels expressed in Xenopus laevis oocytes*(Thomas et al, 2003). *Therefore, tamoxifen could be a confounding factor in this case. When the case is assessed using the French tool of causality assessment the outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Drollmann et al (2014) Glycopyrronium does not affect QT interval in healthy subjects: a randomized, three- period, cross-over, placebo- and positive-controlled study.

Objective: Glycopyrronium (NVA237), a once-daily long-acting muscarinic antagonist, has recently been approved for the treatment of patients with chronic obstructive pulmonary disease (COPD). This study evaluated the effect of glycopyrronium on the QT interval and other cardiac parameters in healthy subjects. Method: This randomized, partially blinded, single-dose, placebo- and positive- (moxifloxacin) controlled, three-way cross-over study investigated the effect of a single inhaled supra-therapeutic dose (8-fold clinical dose in COPD patients) of 400 µg glycopyrronium on the Fridericia-corrected QT interval (QTcF; primary objective), Bazett corrected QT interval (QTcB), heart rate, blood pressure, pharmacokinetics (PK), safety, and tolerability. Results: A total of 73 healthy male (n = 35) and female (n = 38) subjects, aged between 18 and 45 years, were randomized. Glycopyrronium did not cause significant QTcF prolongation compared to placebo. The largest time-matched mean difference to placebo was 2.97 ms at 5 minutes, with the upper limit of the two-sided 90% confidence interval (CI) being 4.80 ms, excluding a relevant QT effect as defined by the ICH E14 guideline. Glycopyrronium had a slight bradycardic effect with a mean change of -2.88 (90% CI: -3.78, -1.99) beats per minutes (bpm) and a maximum of -5.87 (90% CI: -7.82, -3.92) bpm at 5 hours post-inhalation. No clinically relevant effects were seen on QTcB, other electrocardiogram (ECG) intervals, or blood pressure. Maximum plasma concentration (Cmax) of glycopyrronium was achieved shortly after inhalation (median tmax = 7 minutes). All the treatments were well tolerated with no serious adverse events. Conclusion: A supra-therapeutic dose of glycopyrronium had a favorable cardiovascular safety profile with no clinically relevant effect on QT interval. (Drollmann et al, 2014a)

Reviewer conclusions: *This study provides reassurance about the cardiovascular safety inhaled glycopyrronium when given to healthy subjects between 18 and 45 years of age.*

Drollmann et al (2014) Effect of dual bronchodilation with QVA149 on cardiac safety in healthy volunteers.

Objectives: QVA149 is a dual bronchodilator, containing a fixed-dose combination of the long-acting β2-agonist indacaterol and long-acting muscarinic antagonist glycopyrronium, for the treatment of chronic obstructive pulmonary disease (COPD). Here we assess the potential of QVA149 (440/200 μg) at 4-fold the therapeutic dose for causing cardiac pharmacodynamic (PD) effects. Methods: This double-blind, randomized study estimated the time-matched largest heart rate (HR) change and average HR change (over 24 hours) from baseline for QVA149 vs. placebo in healthy subjects. Similar analyses were done for QVA149 vs. indacaterol 600 μg, glycopyrronium 200 μg, and salmeterol 200 μg. The time-matched and average change from baseline in QT interval corrected for HR using Fridericia's formula (QTcF), effects on serum potassium and blood glucose, pharmacokinetic (PK) parameters, and safety were also assessed. Results: Of 50 subjects randomized, 43 completed the study. QVA149, when compared with placebo, showed the time-matched largest mean increase and decrease in HR of 5.69 bpm and -2.51 bpm, respectively, and average HR change from baseline of 0.62 bpm. QVA149 showed no tachycardic potential compared with indacaterol and no relevant tachycardic effect compared with glycopyrronium. No consistent differences were seen in the time-matched largest mean change and average change from baseline in QTcF for QVA149 vs. other treatments. There were no relevant effects of QVA149 on serum potassium and blood glucose. There was no apparent PK/PD relationship between the observed exposures to indacaterol and glycopyrronium in QVA149 on HR and QTcF. There were no deaths or serious adverse events. Conclusions: Overall, short-term administration of QVA149 showed a good cardiovascular safety and tolerability profile in healthy subjects. (Drollmann et al, 2014b)

Reviewer conclusions*: This study provides reassurance about the cardiovascular safety inhaled glycopyrronium when given to healthy subjects.*

Pleym et al (1999) Ventricular fibrillation related to reversal of the neuromuscular blockade in a patient with long QT syndrome.

A 27-year-old previously healthy woman was admitted to hospital with a diagnosis of acute appendicitis. She specifically had no history of syncope, palpitations or other cardiac symptoms. She had never been investigated with electrocardiography (ECG). The patient received morphine 10 mg and scopolamine 0.4 mg i.m. as premedication, and she was treated with 1000 ml of Ringer's solution intravenously before surgery. She was very anxious about the coming anesthesia and surgery, and this state of mind continued also after premedication was given. The patient had a white blood cell count of 13.8xlO"/l and a C-reactive protein concentration of 14 mg/1. Other laboratory tests were within the normal range, except the serum potassium concentration which was 3.3 mmol/1. In the operating theater, the patient was monitored with ECG, pulse oximetry, capnography and non-invasive arterial blood

pressure measurements. Preoxygenation was carried out, and the patient received fentanyl 100 pg, thiopental 300 mg and suxamethonium chloride 70 mg i.v. for a rapid sequence induction. The trachea was easily intubated. Anesthesia was maintained with sevoflurane and N2O in 33% oxygen. Before surgery, rocuronium bromide 40 mg and fentanyl 150 |ig were given. The surgery was uneventful and lasted for 12 min, only. An inflamed appendix was found and removed, and the patient was given metronidazole 1500 mg. Before the end of the surgery, sevoflurane was discontinued and, 20 min later, N2O was stopped. Three to four minutes thereafter, the patient was given glycopyrronium bromide 0.5 mg and neostigmine 2.5 mg i.v. She soon regained spontaneous ventilation, opened her eyes and seemed awake and ready for extubation. It was then suddenly noticed on the ECG monitor that the patient had developed a ventricular fibrillation. She stopped breathing spontaneously, and no pulse could be felt in the carotids or in the femoral artery. Cardiopulmonary resuscitation was started immediately and a cardioverter was called for. As it arrived at the operating theater 1-2 min later, the patient spontaneously returned to a sinus rhythm with normal arterial pulses. The patient regained spontaneous breathing and approximately 30 min later she could be extubated. During the next 3-4h, she was somewhat agitated and she was therefore repeatedly treated with small doses of morphine and diazepam intravenously. She also had episodes of ventricular extrasystoles. A few hours later she was awake and it became obvious that she had come through the event without neurological damage. Preoperatively (8 h before the arrhythmia) her serum potassium concentration was 3.2 mmol/1. Postoperatively (4 and 10 h after the arrhythmia), it was 3.6 mmol/1. Her serum magnesium level was not investigated preoperatively; postoperatively the total serum levels were 0.66 and 0.74 mmol/1, respectively. With the exception of the white blood cell count and the C-reactive protein concentration, all other laboratory tests were normal. Three hours postoperatively, investigation with echocardiography was normal. However, an ECG recording displayed a prolonged QTc interval of 610 ms. The QTc interval was nearly unchanged up to discharge 60 h after the arrhythmia occurred. Nine days later, the QTc interval was shorter but still prolonged, particularly after exercise. Since the basic treatment of LQTS is beta-blockade (1) propranolol 40 mg thrice daily (2 mg per kg body weight per day) was started 30 h after the arrhythmia occurred, and has thereafter been continued. The patient has not experienced any palpitations or syncope attacks during the follow-up period of more than a year. ECG investigations from her only child, her parents, her brother and her four grandparents (two of whom were deceased, but ECG recordings were obtained from their medical records) were all normal. (Pleym et al, 1999)

Reviewers comments: *In this report, the patient had an undiagnosed LQTS which resulted in an episode of cardiac arrest during the final part of general anesthesia, immediately after the drugs for reversal of the neuromuscular blockade were given. The authors say that the administration of glycopyrronium might have been the provoking factor in this patient. The patient's pre operative hypokalaemia may have contributed. Dechallenge is negative in this case as discontinuation of glycopyrronium did not resolve the prolonged QT. Causality assessment using the French tool assessed as Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Saarnivaara et al (1999) Effects of four anticholinesterase-anticholinergic combinations and tracheal extubation on QTc interval of the ECG, heart rate and arterial pressure.

Background: Imbalance in cardiac sympathetic tone causes prolongation of the QTc interval of the ECG. On the other hand, impairment of the parasympathetic control of the heart rate caused by anticholinesterase-anticholinergic combinations might also affect the cardiac sympathetic tone and hence the QTc interval of the ECG. The main purpose of the present study was to compare the effects of four anticholinesterase-anticholinergic combinations used for the antagonism of the neuromuscular block on the QTc interval of the ECG, heart rate and arterial pressure. Methods: Eighty-four American Society of Anesthesiology class I-II patients (healthy patients or with mild systemic disease) with a mean age of 32 to 37 yr undergoing otolaryngological surgery were randomly allocated to one of the following groups: neostigmine 40 microg/kg+glycopyrronium 8 microg/kg (Ne-Glyc), neostigmine 40 microg/kg+atropine 20 microg/kg (Ne-Atr), edrophonium 200 microg/kg+atropine 300 microg (Edr-Atr (1)), edrophonium 500 microg/kg+atropine 7 microg/kg (Edr-Atr (2)). QTc interval and heart rate were measured by a signal processing method based on an IBM/PC/xT-compatible microcomputer and arterial pressure with a sphygmomanometer at 1-min intervals up to 10 min after the injection of the drugs and immediately and 2 min after extubation. The ECG, lead II, was continuously recorded. Neuromuscular block was measured by a Datex relaxograph. Results: In all groups, the most pronounced increase in both QTc interval, heart rate and arterial pressure occurred 1 min after the study drugs and immediately after extubation. In all groups, the mean QTc intervals at 1 and 2 min after the study drugs and after extubation were longer than the upper limit of the normal range (440 ms). Junctional rhythm occurred in 1 to 3 patients in all other groups with the exception of the Edr-Atr(1) group in which no cardiac arrhythmias occurred. At 1 min, the heart rate in the Ne-Atr group was at a significantly higher level than that in the Ne-Glyc group. From 3 to 6 min, the heart rate in the Edr-Atr(2) group and at 3 min in the Edr-Atr(1) group was at a lower level than the heart rate in the Ne-Glyc group. Conclusion: On the basis of the present results, anticholinesterase-anticholinergic combinations should be avoided in patients having a long QT interval syndrome or a prolonged QT interval from other causes. In addition, the

cardiovascular stimulation caused by tracheal extubation should also be avoided in these patients. (Saarnivaara and Simola, 1998)

Reviewers comments: *This study supports the work by Pleym et al which concluded that glycopyrronium should not be given to patients who have LQTS or QT prolongation due to other factors such as drugs or electrolyte imbalances. This is currently not reflected in the SmPC of injectable glycopyrronium.*

Post-marketing pharmacovigilance data review:

Case 1: regarding a 16-year-old female patient who received Robinul (glycopyrrolate injection) therapy coincident with bilateral sagittal split osteotomy surgery and ten minutes after the start of procedure the patient became acutely hypertensive and experienced sinus tachycardia. Subsequently she experienced fulminant pulmonary edema,hemodynamic instability, myocardial ischemia, cardiac failure, left ventricular contractility decreased/hypokinesis with ejection fraction of 35%, and electrocardiograms indicated a prolonged QT interval. The author stated in this situation, the combination of alpha-agonists and anticholinergic agents could lead to hypertension and sinus tachycardia.

The patient's concurrent illness includes retrognathia (mandibular) for which she was presently undergoing a bilateral sagittal split osteotomy; with a past history of haemolytic uraemic syndrome (at age 3), peritoneal dialysis (at age 3 for a "brief period"), tonsillectomy (2001) and adenoidectomy (2001). There were no previous complications with general anesthesia. Indication for Robinul was preinduction and intubation. Duration of therapy was 1 day. The patient was administered 0.5 mg of glycopyrrolate (intravenous). Additional suspect medication included Phenylephrine, topical Lidocaine, Lidocaine Injection and Lidocaine/Epinephrine (epinephrine/lidocaine). Concomitant therapy included Diazepam, Cefazolin, Dexamethasone, Propofol, Fentanyl, Vecuronium, Isoflurane, Nitrous Oxide and Oxygen. EVENT DETAILS: The patient was taken to the operating room for bilateral sagittal split osteotomy (BSSO) for correction of mandibular retrognathia. She was given 2 mg of intravenous diazepam for anxiolysis. To assist in nasotracheal intubation she was given topical phenylephrine (0.5%, one spray each side), topical lidocaine (40 mg/mL, 2 mL to each nare) and 0.5 mg intravenous glycopyrrolate was administered preinduction. She was given 1 gram of intravenous cefazolin for preoperative antibiotic coverage and dexamethasone 10 mg to minimize postoperative edema. Induction was uneventfully accomplished with intravenous propofol 120 mg, lidocaine 80 mg and fentanyl 100 ug. Muscle relaxation was achieved with 5 mg of intravenous vecuronium. Intubation was uneventful and endotracheal tube placement was verified. Hemodynamically, the patient was stable post induction. Vital signs included blood pressure 125/68 mm Hg, heart rate 68, respirations 12, temperature 35.4 degrees Celsius. and oxygen saturation 100 %. Intraoperatively balanced anesthesia was maintained with isofluorane, nitrous oxide and oxygen. Once prepped and draped, 1% lidocaine with 1:100,000 epinephrine (10 mL) was given for local anesthesia at the surgical site bilaterally. Ten minutes after the start of procedure the patient became acutely hypertensive (hypertension) with persistent blood pressure of 200/100 mm Hg and experienced sinus tachycardia (sinus tachycardia) at a rate of 150. At this time a short acting B1 selective beta-blocker (esmolol 90 mg) was given. An initial bolus of 80 mg titrated over 30 seconds, followed by an incremental dose of 10 mg after 2 minutes, was given in an attempt to control her blood pressure. Approximately 10 minutes later with half of the osteotomy complete, a copious amount of pink frothy exudate was noticed in the endotracheal tube. At this time, her oxygen requirements increased and she was maintained on 100% oxygen to maintain her O2 saturation levels above halted and the endotracheal tube was aggressively suctioned. An intraoperative chest radiograph revealed fulminant pulmonary edema (pulmonary oedema). Electrocardiogram at the time showed global elevation in all ST segments and sinus tachycardia. The patient continued to require endotracheal suctioning, while attempts were made to normalize her blood pressure. Gradually over the next 30 minutes, her hemodynamic instability (hemodynamic instability) had resolved with the restoration of normotension with her blood pressure ranging from 110 to 135/70 mm Hg with a heart rate between 90-110 beats per minute. Intraoperative arterial

blood gases at this time were pH PCO2 42, PO2 301, HCO2 24, base excess -0.5, 02 saturation 100%. Other labs included calcium 1.16, sodium 142, potassium 3.8 chloride 106 and glucose 113 (all units and normal ranges were unspecified). In the absence of increased peak airway pressure with maintenance of normal lung volumes, the possibility of post obstructive pulmonary edema was excluded. A working diagnosis of "flash" (acute onset) pulmonary edema without a clear etiology was entertained at this time. Aggressive diuresis of the patient was begun with 5 mg of intravenous furosemide. With acceptable oxygenation and hemodynamic stability, the procedure was rapidly completed without complication. The patient was uneventfully extubated in the operating room and transferred to the intensive care unit on 100 % nonrebreather mask. The author stated it was a case of intraoperative pulmonary edema and cardiac failure (cardiac failure). Postoperative electrocardiograms indicated a T-wave abnormality and a prolonged QT (electrocardiogram QT prolonged). Cardiac enzymes 1 hour post operatively revealed a troponin level of 3.5 (normal <0.3) indicating myocardial ischemia (myocardial ischaemia). Her troponin level continually rose to a peak value of 8.3 at 17 hours after the opereration. An echocardiogram the next day showed a global decrease in left ventricular contractility/hypokinesis (cardiac failure), with ejection fraction of 35% (ejection fraction decreased). There was no evidence of any underlying structural abnormalities of the heart. With continued medical management and with diuresis to maintain a negative fluid balance, the patient's cardiopulmonary status began to improve. Her oxygen requirement decreased with the resolution of her pulmonary edema. By postoperative day 2, she was maintaining adequate oxygenation levels on room air. A chest radiograph taken on postoperative day 2 showed resolution of pulmonary edema. A follow-up echocardiogram on postoperative day 3 showed a normal ejection fraction of 65% and complete resolution of her wall motion abnormalities. The patient was discharged on postoperative day 4 and was seen on follow-up by both the oral and maxillofacial surgery and cardiology services. Her cardiac function had completely normalized with maintenance of good exercise tolerance. The events were considered to be life threatening and prolonged the hospitalization. The authors conclude although post obstructive pulmonary edema can arise with an endotracheal tube in place, this can be excluded if there is no evidence of elevated peak airway pressures. "In our situation, acute onset pulmonary edema arose intraoperatively, with an endotracheal tube in place, with normal peak airway pressures in an otherwise healthy individual. In light of this we believe that an idiosyncratic response to medications is the most likely etiology. The initial combination of alpha-agonists (epinephrine, phenylephrine) and anticholinergic agents (glycopyrrolate) can, in some individuals, lead to hypertension and sinus tachycardia (drug interaction). Both topical and submucousal administration of these medications can lead to unpredictable serum levels. It has been shown that elevated serum levels of epinephrine can peak up to 15 to 30 minutes after submucousal injection. Both phenylephrine and local anesthetic/vasoconstrictor combinations have separately been linked to cases of severe cardiopulmonary compromise. US-EMA-20111103-bkevhumanwt-132044303

Reviewer comment: *Temporality is very suggestive, dechallenge is positive. In the phenylephrine SPC the most common adverse events of phenylephrine are bradycardia, hypertensive episodes, nausea and vomiting other effects effects which are less common tachycardia, palpitations, hypertension, arrhythmia, angina pectoris, myocardial ischemia which are consistent with the adverse events desciribed above. The event QT prolongation is however not listed for phenylephrine. Therefore while the event is Possibly linked to glycopyrronium, it is more likely to be attributed to phenylephrine in this case.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 2: This report comes from a study and concerns a female patient who was who received dexamethasone 5 mg after the induction of anesthesia and ondansetron (intravenous) 4 mg, 30 minutes before the end of the surgery. The anesthesia was standardized for all patients. Fentanyl citrate 2 ug/kg and propofol 3 mg/kg were used for the induction of anesthesia. Postoperative evaluations were performed by nurse anesthetists. Tracheal intubation was facilitated by the administration of rocuronium 0.8 mg/kg. Anesthesia was maintained by sevoflurane 4-5 % (inspired concentrations) in oxygen. Ventilation was mechanically controlled and adjusted to maintain end-tidal carbon dioxide (CO2) values between 30 and 35 mmHg throughout the surgery. Additional rocuronium was administered as required. For reversal of residual muscle relaxation, the combination of glycopyrrolate 0.6 mg and neostigmine 3 mg were administered intravenously and the trachea was extubated. Analgesia was provided by a PCA pump set to deliver a 1 ml bolus of morphine 1 mg/ml with a 5 min lockout interval. On an unspecified date, the patient had a QTc value longer than 470 ms after he/she arrived in the recovery room (QTc prolonged). No cardiac dysrhythmia was found during this period. During the stay in the recovery room, the patient was continuously monitored with a three-lead electrocardiogram, digital pulse oximetry and noninvasive blood pressure. The patient was observed for 24 hours after surgery. Postoperative variables were collected in the recovery room (2 hours after the end of anesthesia) and every 6 hours (from 8:00 AM to 10:00 PM) in the ward. No more relevant information was available. TW-JNJFOC-20120900578

Reviewer comment: *A temporal association is present and the symptoms are compatible but dechallenge is absent and no medical history or information on concomitant medications if any is given. The outcome is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: refers to male patient with oxygen saturation decreased, cardiovascular disorder, nicotine dependence, peripheral vascular disorder and COPD. He was on Lexapro (escitalopram oxalate) and Onbrez (indacaterol maleate). The patient received Seebri Breezhaler (glycopyrronium bromide) for chronic obstructive pulmonary disease (COPD). On an unknown date patient had raised QT interval (electrocardiogram QT prolonged) and oxygen saturation at 80 percent (oxygen saturation decreased) and his circulation was not very good (cardiovascular disorder). The patient QT interval was monitored weekly (5/50). The oxygen saturation was pre-existant COPD and the circulation was affected. The reporter stated that he had taken the patient off Seebri. Dechallenge was positive. The outcome of the event raised QT interval was completely recovered. AU-002147023-PHHY2014AU125053

Reviewer comment: *Temporality and dechallenge support the association. Citalopram could be an alternate explanation. Outcome of causality assessment Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Active substance	BH criterium	Assessment
Glycopyrronium Bromide (GB)	Strength of association	-1.81 PRR, 3 ADR case reports in Eudravigilance with outcomes Possible (1) and Uncertain (2) -1 literature cases reported by Chiu with inhaler outcome Uncertain -2 literature reports with the injectible by Pleym and Sarrnivara with could provide a basis for adding the warning present in the inhaler SmPC (against the administration of GB in patients with LQTS) to the injectible SmPC which currently does not carry such a warning. -2 studies by Drollmann provide reassurance about CV safety but these were done in young healthy volunteers
	Biological Plausibility	Inhibition of the hERG current was observed but only at concentrations significantly higher than the maximum human exposure (Cmax) at the recommended clinical dose.
	Biological gradient	No increasing QT interval prolongation was seen with increasing doses of glycopyrronim bromide
	Experimental evidence and temporality	Temporal relationships were present in all cases but were not very suggestive except in one case. Confounding factors were present in all the cases. Dechallenge was positive in only 1 case.
	Consistency	Cases occurred with both the inhaler and the injectable preparation. However, all except for 1 causality assessment of post marketing data had outcome Uncertain.
	Specificity	Glycopyrronium bromide is a high affinity muscarinic receptor antagonist. A greater than 4-fold selectivity for the human M3 receptors in the lung over the M2 receptors in the heart has been demonstrated.
	Analogy	Other anticholinergics are not known to prolong the QT interval.
Overall assessment	***In the Eudravigilance database the association was disproportionally reported for this drug over others, and preclinical data demonstrates a mechanism of action although this occurred at plasma concentrations not achieved with therapeutic doses. Literature and case review however do not support the relation. Some evidence exists which forms a basis of extending the warning present in the inhaler also to the injectible, ie against the use of glycopyrronium bromide in patients with LQTS.***	

Appendix 7:

Lacosamide

Lacosamide: Vimpat® tablets (50 mg; 100 mg; 150 mg; 200 mg), syrup (10 mg/ml) and solution for infusion (10 mg/ml).

Mechanism of action: lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid. The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes. (SmPC Vimpat, 2016).

Date EU approval: 29 August 2008

Indication: as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy

Availability in MT: not available on government formulary list, available in private sector.

Currently authorised SmPC wording:

Section	**Wording**
4.2 Contraindications	Not listed
4.4 Warnings	Not mentioned
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

Summary of company preclinical data:

In vitro effect on sodium channels: Lacosamide reduced Na+ current in neuronal but also cardiac cells. Therefore, some effects on cardiac conduction may be expected and have indeed been confirmed in in vivo studies in anesthetized dogs and monkeys. Compounds like phenytoin, lamotrigine and carbamazepine, which reduce cardiac sodium current via fast inactivation, have shown similar effects to lacosamide in non-clinical models. Lacosamide affected action potential duration in cardiac tissue in vitro and sodium current in isolated cells, starting at concentrations which are achieved with the maximum human dose, ie 50 to 60 μmol/L. Effects on sodium current were dependent on membrane potential with higher inhibition at more depolarized potentials, suggesting the possibility of relevant effects under such conditions (eg myocardial ischemia).

In vitro effect on potassium channels: The influence of lacosamide on hERG-mediated potassium current was determined in voltage clamped human embryonic kidney (HEK293) cells that stably express the human-ether-à-go-gorelated gene known as hERG. Onset and steady-state block of hERG tail currents were measured at room temperature (22-25°C) using a pulse pattern consisting of a depolarizing pulse from -80 mV to +20 mV for 2 seconds followed by a repolarizing pulse to -50 mV for 2 seconds. The pulse pattern was repeated at 10-second intervals. Peak tail currents were continuously monitored during the 2-second step to -50 mV until a new steady state was achieved in either vehicle or test compound solution. Lacosamide was tested at concentrations of 10, 100, 300 and 3000 μmol/L. Only a weak inhibition of 7% (n=3) at the highest concentration was determined. Under the same experimental conditions the reference compound terfenadine at 60 nmol/L elicited a potassium current block of 76% (n=2). This value is consistent with published data.

In vivo effects: The potential influence of lacosamide on blood pressure, hemodynamic and ECG parameters was investigated in animal studies with spontaneously hypertensive rats after oral drug administration (blood pressure and heart rate only) and in anesthetized dogs and monkeys after intravenous application.

Cardiovascular assessment during a 12-month study in dogs showed a dose-related decrease in peripheral arterial systolic blood pressure in females on test days 1 and 3 and in test week 13. The decrease started at 10 mg/kg and ranged from -13% to -37% compared to either the control group or the value taken before administration. In males, there was no relevant substance-related effect on blood pressure up to the highest dose tested (25 mg/kg). In contrast to the findings in female dogs, in clinical trials there was a slight increase in blood pressure in volunteers taking LCM 800mg/day (5.3.5.3.2 EP, ISS Section 9.1.4) and a slight increase in the number of diabetic neuropathic pain subjects with markedly abnormal increases in systolic blood pressure. The heart rate was marginally increased in both genders treated with the highest dose of 20/25 mg/kg 2 hours after dosing. The difference to the controls was between +7% and +36%, but not statistically significant at $p \leq 0.01$. Similarly, slight increases in heart rate were also observed in a 1-month dose-range finding study and, though not dose-dependent, a 3-month study. No test substance-related influence was noted for the ECG complexes, ie P segment, QRS complex, QTc and PQ (equivalent to PR) interval. A statistically significant increase of the QTc value for high dose females was caused by relatively low QTc values of the controls and considered to be within the normal range. In a 2-week iv study a single 16 mg/kg female was diagnosed with a second degree AV heart block. The company state that this is an occasional finding in Beagle dogs and therefore usually considered to be of no toxicological significance. However, since effects on cardiac conduction may be expected from the mode of action and cardiovascular effects have

been observed also in safety pharmacological studies and clinical trials, a test substance related effect cannot be excluded.

Reviewer conclusions: *Lacosamide exhibits effects on hemodynamics, more likely to occur in females than males. In vitro investigations of the cardiovascular effects of lacosamide showed that it reduced the action potential duration in cardiac tissue and inhibited sodium current in isolated cells. Effects on sodium current were dependent on membrane potential with higher inhibition at more depolarized potentials. In vivo studies showed decreased cardiac conduction. Lacosamide showed some influence on ECG parameters namely dose-dependent transient increase in PR interval and QRS complex duration which was statistically significant. In the in vivo studies, Lacosamide had no effect on QT and QTc intervals using Fridericia correction at any of the doses tested in male dogs but not in high doses in females. The company's postulate that this finding is due to relatively low QTc in the controls.*

Scientific literature review:

Newey et al (2016): Retrospective review of critically ill patients in Status Epilepticus treated with IV lacosamide. Eighty-four patients in SE (43 F/41 M), mean age 59.6 years, were identified; and 59.5 % had non-convulsive SE. The most common etiologies were ischemic and hemorrhagic strokes. There were no significant changes in serial blood pressure monitoring, PR prolongation, aspartate aminotransferase (AST), or creatinine pre- and post-LCM. There was a significant increase in alanine aminotransferase (ALT) from days 1-7 ($p = 0.031$). Fifty-one patients were LCM-naïve. In these patients, cessation of SE after lacosamide occurred in 15.7, 25.5, 58.8, and 82.4 % by 4, 12, 24, and 48h, respectively.

Reviewers comment: *IV lacosamide appears safe short term in critically ill patients both males and females. The results provide reassurance against QT interval prolongation by Lacosamide.*

Kropeit, et al (2015): In a randomized, double-blind, positive- and placebo-controlled, parallel-design trial, healthy volunteers were randomized to lacosamide 400 mg/day (maximum-recommended daily dose, 6 days), lacosamide 800 mg/day (supratherapeutic dose, 6 days), placebo (6 days), or moxifloxacin 400 mg/day (3 days). Variables included maximum time-matched change from baseline in QT interval individually corrected for heart rate ([HR] QTcI), other ECG parameters, pharmacokinetics (PK), and safety/tolerability. The aim was to determine whether lacosamide prolongs the corrected QT interval (QTc). In the study, the QTcI mean maximum difference from placebo was -4.3 ms and -6.3 ms for lacosamide 400 and 800 mg/day; upper limits of the 2-sided 90% confidence interval were below the 10 ms non-inferiority margin (-0.5 and -2.5 ms, respectively). Placebo-corrected QTcI for moxifloxacin was +10.4 ms (lower 90% confidence bound >0 [6.6 ms]), which established assay sensitivity for this trial. Lacosamide (≤ 800 mg/day) did not prolong the QTc interval. Lacosamide caused a small, dose-related increase in mean PR interval that was not associated with AEs.

Reviewer comment: *This study used healthy volunteers, the patients chareacteristics for sex and weight and BMI were similar. The results provide reassurance against QT interval prolongation by Lacosamide.*

Marilyn et al (2012): No QT prolonging effects where observed in 32 patients treated with Lacosamide. 24 hours after LCM initiation 3 patients developed adverse events of altered mental state, exceptionally prolonged ECG PR interval (212 vs 178 ms baseline) and unexplained thrombocytopenia; and a third patient with dizziness, all of which resolved after drug discontinuation. The authors caution that lacosamide should be used in caution in patients with unstable cardiac condition or where prolongation of the PR is unsafe and with renal impairment.

Reviewer comment: *This study provides reassurance against QT interval prolongation by Lacosamide but concludes that cardiac safety is a matter of concern with this drug.*

Kumar and Jhanjee, (2010): In this drug review paper the authors state that Lacosamide does not have tendency to prolong the QT/QTc interval or QRS duration and cite several studies to support this.

Reviewer comment: *This study provides reassurance against QT interval prolongation by Lacosamide.*

Post-marketing pharmacovigilance data review:

Case 1: concerns a 59-year-old female patient initiated on therapy with Vimpat (lacosamide), at a daily dose of 250 mg (100 mg-0-150 mg) via oral route. Co-suspect medication included levetiracetam at a dose of 1500 mg, twice daily for an unknown indication. On an unknown date, the patient experienced prolongation of QT interval with the measured value amounting to QTc 490 ms. DE-UCBSA-2016031768

Reviewer comment: *Unk time to onset or dechallenge. No cardiac effects expected with levetiracetam according to Keppra SmPC.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 2: Female aged 79 years, with a non-serious QT interval prolonged following administration of lacosamide for epilepsy with a latency of several months after start. There were no medical consequences for the patient. The patient outcome is unknown. Concomitant medications were glimepiride, atorvastatin, acetylsalicylate, lactulose. NL-LRB-112046

Reviewer comment: *Unknown dechallenge. No cardiac effects expected with concomitant drugs.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: Fatal case concerning a male patient who initiated therapy with Vimpat (lacosamide) orally 150 mg twice daily for the treatment of epilepsy on 12-Feb-2010. Co-suspect drug included Dilantin (phenytoin). On an unspecified date, the patient

experienced convulsion, arrhythmia related investigations signs and symptoms, cardiac arrhythmias, cardiomyopathy, noninfectious encephalitis, noninfectious meningitis, noninfectious encephalopathy, delirium, torsade de pointes and QT prolongation. On 05-Apr-2010, therapy with lacosamide was discontinued. The patient did not recover from the events. US-UCBSA-054345

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 4: Case concerns 29-year-old Caucasian female patient with a history of seizures. Concomitant medication included Carbatrol (carbamazepine) for seizure disorder, Cephalexin (cefalexin), Promiseb (emollients and protective) and oral contraceptives. The patient initiated treatment with Vimpat (lacosamide) tablets 150 mg daily from 22-Dec-2011 and then titrated up to 150 mg for the treatment of complex partial seizures and continued till the onset of the event. The patient was on carbamazepine for many years for treatment of seizure disorder and then lacosamide therapy was added. During the first week of Feb-2012, the patient reported to the physician that she was 'experiencing palpitations that were waking her up at night'. According to reporter's notes the patient wore a Holter Monitor on 09-Feb-2012. It was stated that the monitor revealed sinus tachycardia. The patient was referred to cardiologist. The reporter stated that the diagnosis given was sinus tachycardia. On 15-Feb-2012, the patient had started Lyrica (pregabalin) 25 mg in morning and 50 mg in evening orally and was continued on lacosamide. After exposure to lacosamide for 2 months the patient experienced palpitations and an electrocardiogram (ECG) and Holter Monitoring was done which revealed prolonged QT interval. Lacosamide was discontinued and the outcome of event is reported as resolved. US-UCBSA-052136

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Possible but case is not very well documented.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2

Result	I2	Possible

Case 5: concerns a 48 year old patient multiply disabled who was initiated on lacosamide on 05-May-2009, orally at a dose of 150 mg twice daily for epilepsy. On 05-May-2009, the QTc time in ECG was 420ms. After ECG, up titration of lacosamide was commenced to 250 mg. On 28-May-2009, the QTc time in ECG was 462ms (21% increase) when the dose was 250 mg. Lacosamide dose was still uptitrated to 300 mg. On 23-Oct-2009, the QTc time in ECG was 433ms (113%) when the lacosamide dose was 300 mg. DE-UCBSA-087506

Reviewer comment:

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 6: concerns 27 year old female patient presented to the emergency room in status epilepticus (SE). She received propofol infusion, levetiracetam and clobazam. On day 3, cardiac monitoring showed an increased QTc of 685 ms, in combination with an abnormal arterial blood gas revealing a metabolic acidosis (pH 7.28, pCO2 33 mm Hg, pO2 133 mm Hg, HCO32 15.5 mEq/L). Arterial lactate increased to 3.7 mmol/L (normal less than 1.6) and creatine kinase increased to 3,037 U/L (normal: 35-170). A diagnosis of propofol-related infusion syndrome (PRIS) was made. Propofol was thus discontinued after a 69-hour infusion and midazolam was initiated, as well as hemofiltration. The PRIS resolved the next day, but the SE was found to be less responsive to midazolam and required dosages up to 100 mg/hour. The SE was not fully controlled on subsequent days and ketamine at an unknown dose via unknown route was added to the drug regimen on day 12. From that point to day 68, she received numerous approaches to control the refractory SE, which included valproic acid, topiramate, lacosamide, magnesium sulfate and dexamethasone. Pentobarbital (manufacturer unknown) and ketamine were the only drugs successfully controlling the SE. On day 30, two previously reported pathologic mutations (c.1880 g-a and e.3287 g-a) were discovered from POLG1 gene test. Valproic acid was stopped at this point. On day 68, an ultimate trial with Isoflurane was proved ineffective once again at drug weaning. The patient died 75 days following admission. CA-EMA-20150508-ssharmap-180705759

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Unlikely. The QT interval had increased to 685ms prior to the start of lacosamide therapy.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Impossible	Symptoms	Compatible
Rechallenge		Lab Test	L0
Dechallenge	C0	Alternate	S1
Result	I0	Unlikely	

Case 7: This case comes was published in the literature by Parekh VB, Bailey JL. Lacosamide intoxication Induced Acute Kidney Injury in a Suicide Attempt by an 18-year-old Woman. J Am Soc Nephrol 2014; 25:995A and concerns an off-label use for dose (12 g) for lacosamide in an 18-year-old female patient who overdosed herself with 12 g of lacosamide in a suicide attempt. The patient had presented 45 minutes after intentional ingestion and had an episode of 15 minutes generalized seizure and prolonged QT interval. Concomitant drugs included: Divalproex sodium-DR (valproate semisodium),Lamictal (lamotrigine), Folic acid, Topamax (topiramate), Ergocalciferol, Depakote (valproate semisodium).Her course was complicated by coma, respiratory failure requiring mechanical ventilation, shock requiring IV pressors, and acute kidney injury (AKI) with anuria and severe acidemia managed initially with a session of hemodialysis (HD) then continuous renal replacement therapy (CRRT) for 60 h followed by a session of HD. On presentation, the pH, bicarbonate, lactic acid were 6.9 (units unspecified), undetectable, 19.2 mmol/L, respectively which corrected to 7.44 (units unspecified), 24 mg/dL and 7.05 mmol/L respectively. The serum BUN, Creatinine, potassium levels were 7 mg/dL, 1.09 mg/dL and 2.8 mmol/L respectively. Urine demonstrated 3-5 coarsely pigmented granular casts consistent with acute tubular necrosis (ATN). Complete clinical recovery occurred after several days of supportive care. The serum creatinine level on presentation was 1.09 mg/dL which peaked at 19 mg/dL before returning to 1.2 mg/dL in about 45 days post ingestion. This case highlights how lacosamide intoxication can result in AKI requiring CRRT and HD (haemodialysis). After oral intake of LCM, it peaks in 1-4 h and has a 13 h elimination half-life. In our patient, lacosamide intoxication may have induced cardiac dysfunction by its direct action on cardiac sodium channels, as a result, reduced cardiac output, leading to hypotension and acute tubular necrosis. Thus, patients initiated on lacosamide therapy should be alerted of the potential complication of acute kidney injury as a result of intoxication with lacosamide. The case also underscores how the clinical course of acute kidney disease after lacosamide intoxication and its management is still unclear and warrants further research. At the time of this report, the events of suicide attempt, coma, respiratory failure, shock and acute kidney injury were resolved.

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Possible. Concomitant drugs are not known to cause QT change. The*

massive overdoses of lacosamide and effects on sodium channels are more likely causes of prolonged QT.

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Sympto ms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 8: Case concerns a 68 years-old Caucasian male subject from Germany with a medical history of arterial hypertonia, obesity and epilepsy. Concomitant medications included amlodipine, hydrochlorothiazide, simvastatin, Pantodac (pantoprazole) and candesartan.In Aug-2013, the subject received Vimpat (lacosamide) in the trial SP1065 A non-interventional, observational study evaluating changes in total drug load and seizure frequency using Vimpat (lacosamide) in daily clinical practice in Combination Therapy with sodium channel blocking anti-epileptic Drugs (AEDs) or non-Sodium channel blocking AEDs at a dose of 100mg twice daily for the treatment of epilepsy". Two months later, on 25-Oct-2013, the subject experienced palpitations. ECG showed a recently developed AV-Block first degree and QTc elongation to 440ms. DE-UCBSA-103584

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Possible but case is not very well documented.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Sympto ms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Active substance	BH criterium	Assessment
LACOSAMIDE	Strength of association	1.02 PRR, 8 ADR Case reports of which 3 were assessed to have a possible causality. Ample literature exists on lacosamide efficacy and safety but none reported QT prolongation. In a through QTc study to determine whether lacosamide prolongs the corrected QT interval, lacosamide at supratheraeupeutic doses did not have an effect on QT.
	Biological Plausibility	Lacosamide did not prolonged QT and block hERG channel, Ikr current in *in vitro* laboratory models. In animal *in vivo* experiments, the statistically significant increase of the QTc value for high dose females was caused by relatively low QTc values of the controls.
	Biological gradient	No dose dependant blockade of I_{Kr} was observed.
	Experimental evidence and temporality	8 post marketing cases were assessed. 3 cases were seen as possibly related to lacosamide but two were not very well documented and the other was in the context of a massive overdose. The remaining 6 cases were seen as uncertain or unlikely to be linked due to late onset of event in 1 case, presence of concomitant drug with known risk for arrhythmias and QT prolongation in 2 cases, lack of temporality and an inverse dose relationship (ADR improved when dose was increased).
	Consistency	No pattern of consistency could be observed.
	Specificity	In preclinical data only a weak inhibition of 7% (n=3) at the highest concentration was determined. Under the same experimental conditions the reference compound terfenadine at 60 nmol/L elicited a potassium current block of 76% (n=2). Lacosamide was found to shorted the AP duration which does not provide a plausible mechanism for QTc interval prolongation.
	Analogy	Lacosamide is a second generation anti epileptic drug (AED) with novel mechanisms of actions. that may be suitable for use with uncontrolled partial-onset epilepsy. There is no apparent analogy in the efficacy or safety parameters of lacosamide when compared to other AEDs.

Overall assessment	***In the Eudravigilance database the association was disproportionally reported for this drug over others. However literature and case review do not support a relationship with QT prolongation, and preclinical data does not adequately demonstrate a mechanism of action.***

Appendix 8:

Levetiracetam

Levetiracetam

BH criterium	Assessment
Strength of association	1.33 PRR 19 ADR assessable cases 6/19 probable or possible (presented here), 13 uncertain (appendix). 2 case reports in the literature with outcome probable (presented here) **Issa et al (2015) QT interval prolongation in a patient with LQT2 on levetiracetam.** Presents the case of a 24-year old female with a seizure disorder and previously undiagnosed long QT syndrome whose QT interval increased and developed into torsades de pointes after her levetiracetam dose was increased. The patient had been having seizures since age 10. The episodes typically occurred in the early morning and witnesses describe shaking of her entire body, incontinence, and while the patient was not aware of the events at the time when they occurred, she did get tired and confused after the events. She had been started on carbamazepine as a child, with escalating doses as she aged. She presented to the NorthShore epilepsy clinic for the first time after a generalized seizure, and was started on levetiracetam 250 mg twice a day with the plan of increasing the dose over weeks then weaning her carbamazepine (initial random carbamazepine level was 10.1 mg/ml). A brain MRI showed minimal T2 hyperintensities in white matter which were interpreted as non-specific. Her EEG showed intermittent right temporal sharp waves with an electrophysiological maximum at T4 and occasional right-temporal polymorphic theta-range slowing suggestive of mild focal cerebral dysfunction. While seizures have not been captured on EEG, the combination of her clinical presentation and focal abnormalities on EEG suggests she has an epileptic disorder. At one-month follow up her serum levetiracetam level was 8.1 mg/ml, and an ECG showed a QTc of 520 ms. She was referred to cardiology for evaluation of her prolonged QT interval. Eleven days later she presented to an outside hospital after a generalized seizure; 3 days before presentation her twice daily levetiracetam had been increased to 500 mg. At that visit to the ED her levetiracetam dose was increased to 1000 mg twice a day and she was discharged home. The following day she presented to the NorthShore ED with complaints of ‘‘difficulty breathing.’’ Initial ECG showed normal sinus rhythm with a QTc of 771 ms . Her levetiracetam level was 34 mg/ml and carbamazepine level was 8.1 mg/ml. While in the ED her mental status deteriorated and her heart rhythm changed into polymorphic ventricular tachycardia/torsades de pointes. She was treated with a lidocaine drip which had almost no effect, and intravenous magnesium sulfate was more effective at terminating the rhythm, but the rhythm recurred, requiring multiple cardioversions. The patient also developed sustained monomorphic ventricular tachycardia of varying morphologies that appeared to initiate with PVCs suggestive of early

after depolarizations. Because of concerns of recurrent hemodynamic collapse she was intubated and sedated; a continuous infusion of magnesium sulfate was used to control her ventricular arrhythmias and her anti-epileptics were discontinued. The day after presentation her QTc decreased to 670 ms with a levetiracetam level of 2.7 mg/ml and carbamazepine level of 4.9 microgram /ml, on subsequent days her levetiracetam level became undetectable (carbamazepine was 2.1 microgram/ml the following day, then became undetectable) with lower QT intervals. Her hospitalization was complicated by pneumonia and diabetes insipidus but she was successfully extubated and the following week a dual-chamber defibrillator device was implanted. She recovered to her baseline, and in the 2-year follow up period her seizures have been well controlled on clobazam with no further episodes of ventricular tachyarrhythmia with the LQT2 syndrome that can present with both long QT intervals and seizures. The prolongation of QT interval after increasing the levetiracetam dose was unexpected since levetiracetam has been one of the AEDs thought to have a minimal effect on QT intervals. Siniscalchi and coworkers reported an increase of only about 25 ms in QTc in post-stroke patients treated with levetiracetam. These patients had adult-acquired seizure disorders and are presumed to have had wild-type ion channels. Levetiracetam has multiple proposed mechanisms of action, among them is inhibition of Kv3.1 that like KCNH2 is a delayedrectifier potassium channel. Unlike KCNH2, however, Kv3.1 is widely expressed in brain tissue, is not thought to play a significant role in cardiac conduction, and has different gating kinetics than KCNH2. As a result, it is unknown if levetiracetam would affect either wild-type or mutant KCNH2 channels. Other AEDs do inhibit KCNH2, with phenytoin, phenobarbital, and lamotrigine having the most significant effect. Carbamazepine, which this patient was also taking, has been shown to inhibit KCNH2, but with a high IC50/ unbound therapeutic concentration making it unlikely to be clinically relevant, and the dose of carbamazepine had not been changed in the preceding year. This case raises the possibility that levetiracetam has an unanticipated effect on cardiac conduction in patients with KCNH2 mutations, especially when used in combination with other AEDs. (Issa et al, 2015)

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S2
Result	I3	Probable	

Rojano et al (2011) Levetiracetam: Acquired long QT syndrome (first report) in an elderly patient: case report. An 88-year-old woman with a history of arterial hypertension and front temporal meningioma, was

admitted with disorientation, automatisms and tonic-clonic movements. Her medications included aspirin and hydrochlorothiazide. Following the onset of generalised seizures, IV levetiracetam 500mg every 12 hours was initiated. She was asymptomatic after 24 hours; however, ECG revealed sinus bradycardia with a corrected QT interval of 480ms. Further investigation showed mild tricuspid insufficiency with short periods of atrial fibrillation. Levetiracetam was withdrawn and valproic acid was initiated. Her ventricular repolarisation corrected after 48 hours. (Rojano Martin et al, 2011)

Reviewer's comments: *Close temporal association is very suggestive, and a positive dechallenge occured. Using FCA the outcome is Probable.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S2
Result	I3	Probable	

Post-marketing cases:

Case 3: concerns 88-year-old female patient with a medical history of hypertension and fronto-temporal meningioma with surgery performed. The patient was concomitantly treated with acetylsalicylic acid and hydrochlorothiazide. The patient went to Emergencies Services due to a switch-off episode along with mouth facial movements of sucking of one minute duration and completely recovered after a postictal state. The patient was checked and the vitals constants and the exploration were normal. In the complementary tests, with a hemogram and plasma biochemistry tests: glycemia was evaluated; renal and hepatic profiles and ions (sodium, potassium, calcium and magnesium) were in a normal range. An EEG and a cranial axial computerized tomography were performed which revealed a left fronto-temporal cranial malacia. During her stay at emergencies, the patient presented with a new switch-off episode with automatisms, followed by tonic-clonic movements. She was diagnosed with complex partial seizures that evolved to generalized seizures, a treatment was started with keppra (levetiracetam) at 500 mg twice daily intravenously. After 24 hours, the patient was found to be asymptomatic, but sinus bradycardia (55 bpm) and a corrected QT interval (Bazett formulae) of 480 msec were found in the ECG. An electrocardiogram and a electrocardiographic holter of 24 hours were solicited and the results showed bradycardia and auricular fibrillation. Levetiracetam was withdrawn and valproic acid was introduced. With that, the ventricular repolarization alterations were corrected. After 48 hours, the reporter assessed the events to be related to levetiracetam. ES-UCBSA-012059

Reviewer comment: *Strong temporal relationship, dechallenge is positive*

and no alternate explanations pointed out. Bradycardia and atrial fibrillation were noted post dose.

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S1
Result	I3	Probable	

Case 7: The patient was commenced on levetiracetam as adjunctive therapy for worsening seizure control of nocturnal complex partial seizures in sleep. Patient had been stable until post-partum 5 months. Before starting levetiracetam there was a sudden re-emergence of seizures in sleep which had been stable on lamotrigine 350mg per day. The dose of lamotrigine had been increased by 50mg during pregnancy because of a drop in lamotrigine level, without consequence. She was advised post-partum to start reducing lamotrigine slowly to pre-pregnancy level, which she then proceeded to do but seizures occurred. However the seizure semiology changed to being a possible generalised seizure than complex partial. Lamotrigine was titrated back up (in accordance with Scottish Intercollegiate Guidelines Network guidelines). Since further increase did not lead to seizure control and lamotrigine levels were within the normal range although at the higher end, levetiracetam was added. It was titrated up slowly due to ongoing events in sleep. No daytime events occurred. Finally she had a very severe generalised seizure based on husbands description and then had a cardiac arrest (husband could not feel a pulse). Husband commenced cardiopulmonary resuscitation. Paramedics recorded Torsade de Pointes and administered 5 shocks. Transferred to emergency department and intensive therapy unit. Further episodes of Torsade de Pointes and the long QTc found on electrocardiogram. Levetiractam thought to possibly be causal and discontinued. Implantable cardioverter defibrillator inserted because of further cardiac arrest on intensive therapy unit post discontinuation of levetiracetam. Patient made full recovery and is on zonisamide and lamotrigine now, seizure free. QTc remains prolonged but not as much as when on levetiracetam. No family history of long QT but all family being seen by cardiologists. Medically Significant Details: A baseline electrocardiogram was not done before prescribing levetiracetam. The QTc was very prolonged (~630msec) on levetiracetam but did not fully correct as post-levetiracetam it remains prolonged (~540msec). GB-MHRA-EYC 00142182

Reviewer comment: *Temporality very suggestive but dechallenge is not entirely positive. A case of long QT syndrome unmasked by event is suggested.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 11: hospital pharmacist reported that a 78-year-old male ICU patient experienced a QTc prolongation while being treated with Keppra (levetiracetam). After Keppra cessation the change in QTc reversed.DE-UCBSA-8040297

Reviewer comment: *Temporality positive and dechallenge positive.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 16: 56-year-old male patient was treated with Keppra (levetiracetam) film-coated tablets 250 mg twice daily for epilepsy from 19-Aug-2009. Patients medical history included chronic renal impairment and pneumonia. The patient was initially admitted to a neurology ward on 15-Nov-2010 with a complex epileptic seizure. He was treated with Keppra and, in the emergency unit was treated with IV NaCl. The patient was planned to be discharged because of significant clinical improvement, but on 19-Nov-2010 his general condition was found to deteriorate abruptly for no apparent reason, with reduced vigilance, hypotension, pallor, thrombopenia, disturbed coagulation, hypothermia (32°C), anuric acute renal failure, skin exanthema, and prolongation of the QTc interval (549 ms, normal range: <450 ms). In addition, he was diagnosed with bradycardia: 38/min. He was then transferred to an internal medical intensive care unit. Potassium levels were at 5.5 mmol/l (normal range: 3.6 - 4.8 mmol/l). On 21-Nov-2010 bradycardia had resolved and heart rate was 77 per min (60 100). Follow-up ECGs indicated that the QTc interval was normalising. On 13-Dec-2010 electrocardiogram QTc interval prolongation had resolved. During the further course, the patient's clinical condition did improve, with the result that he could be transferred to an early geriatric rehabilitation hospital on 30-Dec-2010. At the time of this report, levetiracetam was discontinued and the events general condition deteriorating, reduced vigilance, hypotension, pallor, thrombopenia, disturbed coagulation, hypothermia (32°C), anuric acute renal failure and skin exanthema were resolving. The causal relationship between the events QTc interval prolongation and bradycardia

with levetiracetam was assessed as possible. On 18-Mar-2011: case was repoened to add the reporter's causality for this following event "Long QT-Syndrome" was related. Other Relevant History text: Ex-Smoker (up to 1979, at last 5 cigarettes daily); alcohol abuse up to 2002. DE-FAKOS-150052

Reviewer comment: *Temporality compatible, dechallenge positive, no alternate explanation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S2
Result	I2	Possible	

Case 20: concerned a female patient from Switzerland. The patient was concomitantly treated with Dilatrend (carvedilol), amlodipine, Co-lisinopril (lisinopril+hydrochlorthiazide) for arterial hypertension, Diamicron (gliclacide) for diabetes mellitus and Temesta (lorazepam) for epileptic seizure. The patient initiated treatment with Keppra (levetiracetam) from 08-Sep-2011. On 11-Sep-2011, the patient experienced QT corrected (QTc) prolongation. Treatment with levetiracetam was discontinued on the same day. Magnesium was at 0.69 mmoL/L, creatinine was at 121umol/l and potassium was at 3.8 mmol/l. On 12-Sep-2011, QTc was 570 ms. On 13-Sep-2011 QTc was 360 ms, the patient was treated with Depakene chrono (sodium valproate) 500 mg twice daily for epileptic seizure. The patient was recovering from the event at the time of the report. The physician assessed the causal relationship between the drug and the event was possible. Patient experienced the event after approximately 3 days of exposure to levetiracetam. Dechallenge positive on drug withdrawal. CH-UCBSA-041397

Reviewer comment: *Temporality suggestive, dechallenge positive and there does not appear to be an alternate explanation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Very suggestive	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C3	Alternate	S2
Result	I3	Probable	

<table>
<tr><td></td><td>
Case 23: This report concerns a 50-year-old male patient from Germany. The patient initiated treatment with Keppra (levetiracetam) film-coated tablets at a dosage of 3000 mg daily. The patient experienced QT prolongation in the ECG (electrocardiogram). Treatment with levetiracetam was discontinued immediately. The reporting hospital cardiologist reported that as of Aug-2012, the patient recovered from QT prolongation. In the physician’s opinion, the causal relationship between levetiracetam medication and the event was assessed as “possible. DE-UCBSA-064429

Reviewer comment: Positive dechallenge and no alternate explanation make this case possible related.
<table>
<tr><td colspan="4">Causality Assessment (French Method)</td></tr>
<tr><td colspan="2">Chronological criteria</td><td colspan="2">Semiological criteria</td></tr>
<tr><td>Challenge</td><td>Compatible</td><td>Symptoms</td><td>Compatible</td></tr>
<tr><td>Rechallenge</td><td>R0</td><td>Lab Test</td><td>L0</td></tr>
<tr><td>Dechallenge</td><td>C2</td><td>Alternate</td><td>S2</td></tr>
<tr><td>Result</td><td>I2</td><td colspan="2">Possible</td></tr>
</table>
</td></tr>
<tr><td>Biological Plausibility</td><td>The preclinical data submitted in this generic dossier was insufficient to characterise any effects on hERG.</td></tr>
<tr><td>Biological gradient</td><td>Increased QT interval prolongation was not observed with increasing dose of levetiracetam, however, in cases where QT interval prolongation occurred, reducing the dose, reduced the QT effect in the post marketing cases (positive dechallenge).

Direct hERG inhibition data is not available for this product.</td></tr>
<tr><td>Experimental evidence and temporality</td><td>Of the 19 cases assessed for QT prolongation, the majority had a temporal relationship between the events and the initiation of treatment. 13 cases had confounding factors, negative dechallenge or presence of electrolyte imbalances and some occurred in the presence of underlying cardiac conditions

3 post marketing studies, 2 supporting causality of levetiracetam with QT prolongation are presented here:

Siniscalchi et al (2014) Effects of phenobarbital and levetiracetam on PR and QTc intervals in patients with post-stroke seizure.

Sudden unexplained/unexpected death (SUDEP) is related to high mortality in patients with epilepsy. The prolongation of QT interval, involved in cardiac arrhythmia-related SUDEP, may be precipitated by antiepileptic drugs (AEDs). In this study, we evaluated the effects of phenobarbital</td></tr>
</table>

and levetiracetam on PR-QTc intervals in patients with post-stroke seizures. Methods: An open-label, parallel group, prospective, multicenter study between June 2009 and December 2013 in patients older than 18 years of age with a clinical diagnosis of post-stroke seizure and treated with phenobarbital or levetiracetam. In order to exclude a role of cerebral post-stroke injury on modulation of PR and QTc intervals, patients with cerebral post-stroke injury and without seizures were also enrolled as controls. Results: Interictal electrocardiography analysis revealed no significant difference in PR interval between patients treated with an AED (n = 49) and control patients (n = 50) (181.25 ± 12.05 vs. 182.4 ± 10.3 ms; $p > 0.05$). In contrast, a significantly longer QTc interval was recorded in patients treated with an AED compared with control patients (441.2 ± 56.6 vs. 396.8 ± 49.3 ms; $p < 0.01$). Patients treated with phenobarbital showed a significantly longer QTc interval than patients treated with levetiracetam (460.0 ± 57.2 vs. 421.5 ± 50.1 ms; $p < 0.05$). Conclusions: The study reported that in patients with late post-stroke seizures, phenobarbital prolonged QTc interval more so than levetiracetam. (Siniscalchi et al, 2014)

Reviewer's comments: *This study demonstrated a QT prolongation effect of levetiracetam when used in post stroke epileptic patients (Group B; 421.5 ± 50.1 ms) [p\0.05] compared with the control group (p\0.01). A QTc interval over 480ms was observed in 4 patients treated with levetiracetam, one of which had a QTC over 500ms. This study adds evidence to a QT prolonging effect with levetiracetam.*

Krishnan et al (2013) Interictal 12-lead electrocardiography in patients with epilepsy. (Krishnan and Krishnamurthy, 2013)

Interictal electrocardiographic predictors of sudden unexpected death in epilepsy (SUDEP) are unknown. This study was designed to identify the unique features of the interictal 12-lead electrocardiogram (EKG) in patients with epileptic seizures. We conducted a retrospective chart review of adult patients below the age of 65 admitted to our epilepsy monitoring unit. Using EEG telemetry data, we classified patients as having nonepileptic seizures (NESs), probable epilepsy (PE), or definite epilepsy (DE) and analyzed 12-lead EKGs obtained on admission. Patients with NESs were assigned as the control group. We included patients taking antipsychotic and/or antidepressant medications but excluded patients with medical conditions or taking other medications that would otherwise confound EKG measurements. Out of the 1007 charts reviewed, 195 patients were included in our analysis, and extensive subgroup analyses were performed. We found that patients with definite localization-related epilepsy displayed a significantly longer average PR interval (162.1 ms) than patients with NESs (148.8 ms). This effect was pronounced in female patients and did not vary with the number of antiepileptic drugs (AEDs) prescribed. In contrast to previous studies, mean QTc intervals were not significantly different between DE (428 ms) and NESs (422.6 ms). However, within females, this difference reached statistical significance (DE: 434.6 ms, NESs: 424.6 ms). Antiepileptic drug polytherapy was associated with a significantly lower QTc interval (416 ms in patients on 4-6 drugs and 436.4 ms in patients on 0-1 drugs). Levetiracetam was the most commonly used AED and was associated

	with the longest average PR (163 ms) and QTc (432 ms) intervals. The mean QRS axis displayed a significant leftward shift in patients with localization-related epilepsy (35.6° versus 54.3° in patients with NESs) and also in female patients with DE (42.1° versus 55.4° in female patients with NESs). No differences were observed between patients with left versus right hemisphere seizure foci. Overall, these findings may reflect cardiac structural changes and/or alterations in autonomic tone that deserve closer study. Further, longer-term prospective studies are required to understand how these electrocardiographic signatures may predict sudden unexpected death in epilepsy. (Krishnan and Krishnamurthy, 2013) ***Reviewer's comments:*** *In this study authors report that Levetiracetam, the most commonly used anti-epileptic drug in this study was associated with the longest average QTc (432 ms) intervals.* 1 company study showed no association **Hulhoven et al (2008) Effect of levetiracetam on cardiac repolarization in healthy subjects: a single-dose, randomized, placebo- and active-controlled, four-way crossover study.** Non-antiarrhythmic drugs may have the potential to prolong the QT interval, leading to potentially fatal ventricular tachycardias, including torsades de pointes. Objectives: This study evaluated the potential of the newer-generation, multiple-action antiepileptic drug levetiracetam, which binds to the synaptic vesicle protein SV2A, to affect cardiac repolarization, as detected by prolongation of the QT/corrected QT (QTc) interval. Methods: This was a single-dose, randomized, placebo- and active-controlled, 4-way crossover study in healthy subjects. Subjects were randomly allocated to 1 of 4 different administration sequences. Each sequence included 3 double-blind treatments (levetirace-tam 1000 mg, levetiracetam 5000 mg, and placebo) and 1 open-label treatment (moxifloxacin 400 mg). Triplicate electrocardiograms (ECGs) were obtained at baseline and at various time points over 24 hours after each treatment using continuous Holter monitoring. ECGs were read centrally in a blinded manner. Blood samples for the determination of plasma concentrations of levetiracetam and moxifloxacin were collected before dosing and at 0.5, 1, 1.5, 2, 4, 6, 12, and 24 hours after dosing, within 5 minutes after the ECG recordings. The QT interval was corrected for heart rate using a sex- and study-specific correction (QTc(ss)) as the primary outcome measure and Fridericia's correction (QTc(F))as a secondary outcome measure. The primary analysis was performed on the time-matched, baseline-subtracted QTc(ss) (DeltaQTc(ss)). The maximum DeltaQTc(ss) difference between each active treatment and placebo (DeltaDeltaTc(ss)) was derived from a mixed-effect analysis of variance. Clinical laboratory tests, standard 12-lead ECGs, and vital signs were monitored at regular intervals. Spontaneously reported adverse events were recorded throughout the study. Results: Fifty-two healthy, nonsmoking subjects (26 men, 26 women; 37 white, 9 black, 3 Hispanic, and 3 Asian/Pacific Islander) with a mean (SD) age of 28.4 (7.5) years (range, 18-45 years) and a mean weight of 71.5 (12.6) kg (range, 49-

	103 kg) participated in the study. Levetiracetam did not significantly prolong the QTc(ss). The upper bound of the 1-sided 95% CI for the maximum DeltaDeltaTc(ss) was 8.0 milliseconds for levetiracetam 1000 mg and 8.1 milliseconds for levetiracetam 5000 mg, with mean estimates of 4.0 and 4.1 milliseconds, respectively; similar results were obtained for the maximum DeltaDeltaQTc(F). Moxifloxacin significantly prolonged the QTc(ss), with a lower bound of the 1-sided 95% CI for the maximum DeltaDeltaQTc(ss) of 3.7 milliseconds and a mean estimate of 7.7 milliseconds. There was no statistically significant relationship between measured DeltaQTc(ss) and the levetiracetam plasma concentration, whereas a significant linear relationship was observed between measured DeltaQTc(ss) and the moxifloxacin plasma concentration (slope estimate: 4.4 milliseconds/[microg/mL]); 95% CI, 3.2-5.7; P < 0.001). No unexpected safety concerns arose based on reported adverse events, clinical laboratory evaluations, physical examinations, vital signs, or ECG monitoring during the course of the study. Conclusion: This randomized, placebo- and active-controlled study in healthy adult subjects found no clinically relevant changes in the QTc interval after a single levetiracetam dose of 1000 or 5000 mg. (Hulhoven et al, 2008) ***Reviewer's comments:*** *This company study found no clinically significant QT prolongation after test subjects were given a single dose of Keppra 1000mg and 5000mg. This study was done in healthy subjects aged between 18 and 45 years with no history of or risk factors for torsades de pointes, including a family history of arrhythmia or sudden death. Therefore, the generalisability of this study is questionable.*
Consistency	A presentation which included bradycardia and hypotension together with QT prolongation was seen in X cases. Literature supports the association. Cases from EU and non EU, doctor, consumer and pharmacist reports make event reporting consistent among a heterogeneous group.
Specificity	Levetiracetam blockade on the hERG potassium channel if any, was not studied.
Analogy	Levetiracetam has a different mode of action from other anti epileptic drugs. No analogy can be accurately made in this case.
Overall assessment: ***In the Eudravigilance database the association of levetiracetam with QT prolongation was disproportionally reported for this drug over others. Literature and case review support a relation between drug and effect. Preclinical data available does not include hERG channel studies.***	

Appendix 9:

Loxapine

Loxapine: Adesuve® inhalation powder 4.5mg and 9.1mg for single use in EU. In France only, 10mg tablets, 1mg oral solution or I.M injection available.

Mechanism of action: the antipsychotic effects of Loxapine may be primarily attributable to its antagonism of dopamine D2 receptors. Loxapine also has 5-HT2A antagonist activity and has anti-cholinergic, anti-histaminergic and anti-alpha-adrenergic properties

Date EU approval: 20th February 2013 (as inhalant), as tablets, oral solution in FR since the 70s.

Indication: for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder.

Availability in MT: not available on government formulary list or private sector.

Currently authorised SmPC wording:

Section	Wording
4.2 Contraindications	*Not listed*
4.4 Warnings	*Clinically relevant QT prolongation does not appear to be associated with single and repeat doses of Adasuve. Caution should be exercised when Adasuve is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation due to interaction with medicinal products known to prolong QTc interval is unknown.*
4.5 Interactions	*Not listed*
4.8 List of ADRs	*Not listed*
5.0 Pharmacology	*Not listed*

Summary of company preclinical data:

In vitro: The effects of loxapine on hERG current expressed in stably transfected human embryonic kidney (HEK-293) cells was studied. Loxapine dose-dependently blocked the hERG current with an IC50 value of 1.8 μM. Thus, loxapine blocks hERG channel current only at relatively high concentrations. A comparison of IC50 values of loxapine and other antipsychotics is given in the Table below.

Comparison of IC_{50} Values at hERG Channel for Loxapine and Other Antipsychotics

Antipsychotic Drug	IC_{50} (nM)	Reference
Sertindole	3	Kongsamut 2002
Droperidol	32	Drolet 1999
Risperidone	167	Kongsamut 2002
Ziprasidone	169	Kongsamut 2002
Thioridazine	191	Kongsamut 2002
Perphenazine	1003	Kim 2005
Chlorpromazine	1561	Kim 2005
Loxapine	1800	Sponsor study[a]
Quetiapine	5765	Kongsamut 2002
Olanzapine	6013	Kongsamut 2002

[a]m4.2.1.3, Study D03.017/1, Section 6.1, Table 1
IC_{50}: concentration causing half maximal inhibition of control hERG current

Effects of intravenous (IV) administration of loxapine in dogs, included transient hypotension, decreased arterial blood flow, increased cardiac contractility and increased cardiac output. Heart rate was not affected by loxapine treatment and there were no consistent changes in ECG parameters. Additionally, the sponsor conducted a GLP cardiovascular and respiratory safety study in conscious (non-anesthetized) telemetered beagle dogs to supplement the data from the literature, and to evaluate rapid delivery of loxapine. Pharmacokinetic profiles of intravenous and inhalation administration in anesthetized dog revealed that IV bolus delivery mimicked exposure by inhalation, providing support for the IV route in the cardiovascular safety study. At intravenous doses of 0.15 and 0.5 mg/kg to conscious dogs, loxapine did not induce cardiovascular changes. At the high dose of 1.5 mg/kg, a transient and mild decrease in blood pressure followed by a transient and mild increase was the only biologically relevant cardiovascular change. No changes in ECG intervals attributable to loxapine were observed and loxapine administration did not lead to QT or QTc prolongation.

***In Vivo* Effects:** In one study, effects of intravenous loxapine (0.1 - 2.5 mg/kg) on carotid blood pressure, femoral blood flow, heart rate, and ECG patterns were studied in anesthetized cats. Loxapine administration produced dose-dependent decreases in carotid blood pressure. Carotid blood pressure returned to baseline 4 minutes following 0.1 mg/kg loxapine, after more than 16 minutes following 0.5 mg/kg loxapine, and after more than 60 minutes following 2.5 mg/kg loxapine. Loxapine had little effect on femoral blood flow at the two

lower loxapine doses, but produced transient and marked decreases (approximately 76%) in blood flow after 2.5 mg/kg, followed 1 minute later by marked increases. Loxapine administration did not have any significant effects on heart rate, PR interval, or ECG patterns.

In another study in anesthetized intact cats, intravenous loxapine administration (0.25 - 5 mg/kg) led to a transient hypotensive response, with an immediate return to control blood pressure values. In decerebrated cats subjected to the same treatment, initial hypotensive response was followed by a period of sustained hypertension which was partially inhibited by the non-selective alpha blocker phenoxybenzamine. Comparable observations after administration of loxapine alone (0.1 – 5 mg/kg) showed that intravenous administration of loxapine (5 mg/kg) in cats did not cause disturbances in cardiac rhythm and that intravenous administration of loxapine (2 mg/kg) did not block or attenuate the vasopressor effects of amphetamine.

In other studies using dose ranges of 0.5 – 4 mg/kg, the effects of loxapine usually trended towards decreased blood pressure, reduced arterial blood flow, increased cardiac contractility, and increased cardiac output. Heart rate was not affected by loxapine treatment and there were no consistent changes in ECG parameters. However, when the dose of loxapine was increased to 7.5 mg/kg (cumulative intravenous dose), one dog developed markedly elevated T-waves and expired in cardiac arrest. In subsequent studies in conscious dogs with loxapine administered orally at doses up to 10 mg/kg/d for 6 months and 20 or 30 mg/kg/d for 3 months, however, it was noted that no clinical or histopathological signs of cardiotoxicity were seen.

In summary, in vivo nonclinical studies indicate no detrimental effects of intravenous administration of loxapine on cardiovascular functions at doses up to 0.5 mg/kg, and a potential for transient hypotension with administration of doses higher than 0.5 mg/kg. In sponsor clinical pharmacokinetic studies in healthy volunteers (n=114), the mean Cmax was 257 ± 219 ng/mL following exposure to a single 10 mg dose of Adasuve® loxapine inhalation powder, pre-dispensed (Staccato loxapine). Therefore, the Cmax for the dose of 0.5 mg/kg in this dog cardiovascular study was more than 5 times greater than seen with a clinical Staccato loxapine dose of 10 mg.

Reviewer conclusions: *Loxapine preclinical studies on hERG channels show a blockade at 1800nM as in the table above. The company comments that this block occurs only at relatively high concentrations. However, comparing the IC50 of loxapine with that of chlorpromazine, the values are not much different. Furthermore there is a steep jump between IC50 of loxapine and quetiapine (IC50 5765nM). Both quetiapine and chlorpromazine have QT prolongation listed in the sections 4.4 and 4.8 of the SmPC. The extent of hERG channel inhibition is a key factor affecting QTc prolongation. The preclinical data for loxapine supports a biological mechanism for QT interval prolongation via hERG inhibition at moderately high doses.*

Scientific literature review:

Cassella, et al (2015): A randomized, placebo-controlled repeat-dose thorough QT study of inhaled loxapine in healthy volunteers.

In this randomized, double-blind, active- and placebo-controlled, crossover, thorough QT study, the effect of two inhaled loxapine doses on cardiac repolarization as measured by corrected QT (QTc) interval in healthy subjects was assessed. Subjects received two doses of inhaled loxapine (10 mg) 2 hours apart+oral placebo, two doses of inhaled placebo+oral placebo, or two doses of inhaled placebo+oral moxifloxacin (400 mg; positive control), with ≥3 days washout between treatments. Two-sided 90% confidence intervals (CIs) were calculated around least-squares mean pre dose placebo-subtracted individually corrected QT durations (ΔΔTcIs) at 12 time points throughout 24 hours after dosing. A ΔΔTcI 95% upper CI exceeding 10 msec was the threshold indicating QTc prolongation (primary endpoint). Secondary endpoints included Fridericia- and Bazett-corrected QT duration and QTcI outliers. Pharmacokinetics and adverse events (AEs) were also assessed. **Results:** 60 subjects were enrolled, mean age, 33.8 years; 52% male), 44 completed the study. Post loxapine dosing, no ΔΔTcI 95% upper CI exceeded 10 msec; the largest was 6.31 msec 5 minutes post dose 2. Methodology was validated by ΔΔTcI 95% lower CIs exceeding 5 msec at 9 of 12 time points after moxifloxacin dosing. Loxapine plasma concentrations increased rapidly (mean Cmax, 177 ng/mL; median tmax 2 minutes after dose 2, 2.03 hours after dose 1). There were no deaths, serious AEs, or AEs leading to discontinuation, and one severe AE. **Conclusion:** Primary and secondary endpoints indicated two therapeutic doses of inhaled loxapine did not cause threshold QTc prolongation in this study.

Reviewer comment: *This company sponsored trial was done to establish the risk of repeat dose (2 doses) loxapine in healthy young males and females since in the EU a second dose of loxapine by inhalation is permitted 2 hours after initial dose in the uncontrolled agitated patient. In this study, the threshold QT was not exceeded using the method of least-squares mean pre dose placebo-subtracted individually corrected QT durations (ΔΔTcIs). However, this study was conducted in healthy young adults and so the results may not be applicable in the wider population with additional factors predisposing to TdP (such as hypokalemia and underlying heart conditions). {{447 Cassella, 2015;}}*

The results of this study do not exclude a risk of clinically significant QT prolongation when loxapine is used in the wider population When considering medications to treat agitation in emergency settings, the risk of QTc prolongation should be considered, especially because additional TdP risk factors such as concomitant drug use, electrolyte disturbances and underlying disease will very often be present.

Spyker et al (2014) Loxapine delivered as a thermally generated aerosol does not prolong QTc in a thorough QT/QTc study in healthy subjects. Forty-eight healthy volunteers received a single inhaled placebo or 10 mg loxapine. Plasma concentrations of loxapine increased with a median Tmax of 1 minute and a mean Cmax of 312 ng/mL. After an initial rapid distribution phase, plasma concentrations of loxapine declined with a terminal half-life of 8 hours. **Results:** Inhaled loxapine did not increase QTintervals, as demonstrated by the upper bound of the 1-sided 95% CIs placed on the point estimate of the placebo-subtracted change of QTcI (ΔΔQTcI) being less than 10 milliseconds at all 11 post-dose times. The maximum ΔΔQTcI occurred at 1 hour post-dose (LSmean 5.42 milliseconds,

upper confidence bound 7.75 milliseconds). The study outcome was validated by the demonstrated assay sensitivity using the positive control moxifloxacin maximum ΔΔQTcI occurred at 3 hour post-dose (LSmean 8.36 milliseconds, lower confidence bound 5.82 milliseconds). **Conclusion:** The analyses of QTc outliers, and the lack of emergent diagnostic findings for QTcI, QTcB, and QTcF; and simple mean placebo-subtracted changes of QTcI and QTcF supported the primary QT analysis conclusion that this is a negative finding and there is no apparent QT prolongation associated with the therapeutic dose of inhaled loxapine. {{449 Spyker,D.A. 2014;

Reviewer comment: *This company sponsored trial was performed in 48 healthy males and females median age 46 years. In this study, the peak moxifloxacin induced QT prolongation following correction for heart rate using the ΔΔQTcI method, was 8.1ms and the method was validated since the lower confidence interval at 90% was greater than 5 ms for the active control. Again this study was conducted in healthy young adults and so the results may not be applicable in the wider population with additional factors predisposing to TdP (such as hypokalemia and underlying heart conditions).*

The results of this study do not exclude a risk of clinically significant QT prolongation when loxapine is used in the wider population. When considering medication to treat agitation in emergency settings, the risk of QTc prolongation should be considered, especially because additional TdP risk factors such as concomitant drug use and underlying disease will very often be present.

Post-marketing pharmacovigilance data review:

Case 1: Male patient, weighing 90kg attempts suicide by ingesting Valium® 10 mg + 1000 mg of Seroquel LP + 1 vial of Loxapac® (loxapine), 10 tablets Nortryptalin and 10 tablets Amitriptylin. When the paramedics came, the patient had neurological symptoms Glasgow scale 7. Heart rate was 100 bpm, the ECG has a sinus rhythm with appearance of the normal P-wave and the limiting PR space (0.20 s); QRS slightly elongated at 0.10 s; No branch block appearance; No Q waves; no S1-Q3; No left ventricular hypertrophy, no Sub-shift of the ST segment. The corrected QT interval lengthened: 500 ms. The toxicological report reports the presence of benzodiazepines and of tricyclic antidepressants in supra-therapeutic doses in the blood. Loxapine = 0.137 mg / L (therapeutic 0.01-0.03), Nortriptyline + amitriptyline = 0.500 mg / L (therapeutic cc 0.12 -0.25), Diazepam + nordiazepam = 0.232 mg / L, No dosage of quetiapine. After 48hrs an episode of sinus tachycardia occurred possibly due to the still toxic levels of tricyclic antidepressants. Outcome is reported as resolved for this patient. FR-AFSSAPS-PA20150126

Reviewer comment: *Case assessed using the French Method of causality assessment. Outcome Uncertain to be related to loxapine. Concomitant drugs in overdose are more likely perpetrators for the event QT interval prolongation.*

Case 2: Case on a 46 year-old male patient who experienced QT interval prolonged following treatment with cyamemazine, loxapine, oxazepam and zopiclone. The case was reported in literature. Patient's was an alcohol consumer, tobacco and cannabis user. On an unknown date, the patient had QT interval prolongation to 450 msec. This case was retrieved from the literature article by Montastruc F, Rieu J, Letamendia C, Montastruc JL, Pathak A, Schmitt L. [Measurement of QT interval and serotoninergic reuptake inhibitor antidepressants: A study in a university psychiatric hospital]. [French]. Encephale 2015;41(3):282-283.

Reviewer comment: *Case assessed using the French Method of causality assessment. The temporal association between the administration of cyamemazine, loxapine oxazepam and zopiclone and the onset of QT interval prolonged suggests an Uncertian causality attribution to loxapine. It is more likely that cyamemazine caused the QT to prolong.*

Case 3: Patient with no cardiac history was hospitalised for syncope after being administered clopixol (zuclopenthixol) and loxapine 25mg for treatment of psychosis and agitation. At the beginning, the patient had a normal hemodynamic state but at an unknown time, an ECG revealed a sinus tachycardia at 100b/ min with a long QT corrected to 490ms. Trans-thoracic ultrasound finds left ventricular function normal without segmental kinetic disorder or valvulopathy An angio-coronary angiograph was performed which revealed healthy coronaries. Low doses of b-blockers (Tenormin 25mg/d) made it possible to completely stop the supraventricular tachycardia as well as the extrasystoles. Outcome resolved. FR-AFSSAPS-NC20090365

Reviewer comment: *Case assessed using the French Method of causality assessment outcome Uncertain. The temporal association between the administration of zuclopenthixol and loxapine and the onset of QT interval prolonged suggests an association, but could be more attributable to concomitant drug which is expected to prolong QT as per SmPC.*

Case 4: 21 year old male presenting with polytoxicomania from ingestion of ketamine, cocaine, heroin and cannabis was resuscitated from bradycardia. QT interval was prolonged at 600ms. He had been sedated previously with tiapridal 600mg, loxapine 50mg, and tranxene 110 mg for aggressiveness 6 hours previously.

Reviewer comment: *Poorly documented case. Concomitant drugs especially Cocaine, bradycardia and overdose are more likely perpetrators for the event QT interval prolongation. Causality assessment using French method: Uncertain.*

Case 5: 76-year-old woman hospitalized for a confusional syndrome presents with a suspected neuroleptic malignant syndrome. Hyperthermia at 38.2 ° C appeared after injection of loxapine. CPK was elevated to 10400, metabolic acidosis with alkaline reserve at 19, troponin at 0.31 and QT elongated and likely hypokalemia responsible for the elongation of the QT segment. Renal function was limited. Loxapine was stopped on 30/03/2008 and patient was rehydrated and an underlying hypokalemia was corrected and controlled. FR-AFSSAPS-TO20100960

Reviewer comment: *French causality assessment outcome is possible for neuroleptic malignant syndrome (NMS) with loxapine which is a listed adverse event. The QT prolongation was a by product of hypokalaemia due to limited renal function caused by the NMS and dehydration. Outcome for QT prolongation directly caused by loxapine is Unlikely in this case.*

Case 6: 42-year-old female patient was started on Seroquel 300 mg per day on 15-FEB-2012. Concomitant medications included sulfarlem (treatment for xerostomia) 12.5 mg three times per day, Prazepam 10 mg twice per day, Zopiclone 7.5 mg per day, Paracetamol 2 tablets every 6 hours if needed and Pravastatin 10 mg per day. On that same day, the patient took one tablet of Loxapac 25mg.On 16-Feb-2012, QT interval was at 474 milliseconds. Dose of Seroquel was increased to 400 mg per day. On 17-FEB-2012, QT interval was at 500 milliseconds. Cardiac auscultation was difficult. Heart sounds were regular without murmur. Blood pressure was kept under closure. On that same day, the patient started Loxapac 30 drops for agitation or insomnia. Dose of Seroquel was reduced to 300 mg per day. On 18-Feb-2012, dose of Seroquel was reduced to 200 mg per day. On 19-Feb-2012, dose of Seroquel was reduced to 100 mg per day. On 20-Feb-2012, dose of Seroquel was reduced to 50 mg per day. ECG evidenced QT interval at 460 milliseconds and sinus tachycardia (110 beats per minute).On 21-Feb-2012, Seroquel was stopped. Dose of Loxapac was increased to 20 drops three times per day. At the time of report, QT interval increase resolved. The reporter suspected Sulfarlem, Prazepam, Loxapac, Zopiclone and

Pravastatin but considered Seroquel as the most suspect drug.FR-AstraZeneca-2012SE22080

Reviewer comment: *French causality assessment outcome is Unlikely. Dose decreases of Seroquel (named Seroquel in MT, Xeroquel in FR) lead to improvement in the QT interval and the introduction and dose increase of loxaopine had no effect. The reporting physician considers Seroquel as the most suspect drug. QT interval prolongation is a listed side effect in the SmPC of 25mg Seroquel.*

Case 7: Literature case concerns a 29 year old female patient who experienced toxicity-induced pulmonary edema, acute cardiorespiratory distress and QT prolongation and subsequently died. On an unknown date, the patient was admitted to hospital and commenced treatment with oral cyamemazine at 100 mg on day 1 and 300 mg on the next day. The patient also took loxapine succinate in case of serious agitation and also received caffeine (dosage regimen and batch/lot number and expiry date unknown). The only abnormality identified was constant tachycardia from the patient's first day in hospital, fluctuating between 100 and 138 beats per minute, usually around 105 beats per minute. On day 3, patient commenced therapy with oral clozapine at a dose of 25 mg and received this until day 8, thereafter at a dose of 50 mg from day 9 to day 13; cyamemazine at 200 mg on day 3, and then 300 mg from day 4 and continued till day 13; 30 drops of oral alimemazine tartrate from day 3 to day 8 and then from day 10 to day 12. Unspecified time later, 13 days after initial admission, the patient suddenly died due to suspected drug interaction between and clozapine and caffeine. Prolongation of the QT interval was seen on the electrocardiogram in this patient. There were no notable somatic or psychiatric factors on the final day of hospitalization. There was no edema in the lips and glottis, and no skin rash, ruling out anaphylactic shock. There was no sign of any blow or violence. The autopsy report indicated intense cyanosis of the face and fingernails. A blood sample was taken, with pulmonary froth present on puncture. A femoral blood sample was taken at the first examination of the body. The autopsy confirmed the lack of any sign of a blow or of violence. The congested appearance of the face and the viscera and the presence of froth in the trachea suggested death due to acute cardiorespiratory distress. The anatomopathological examination revealed moderate uncomplicated cardiovascular atherosclerosis. In the lungs, there was alveolar distension with stretching and rupture of the alveolar walls, and pulmonary edema. Examination of the liver revealed steatosis. Investigation and assay for ethyl alcohol gave a level of 0.01 g/L. In the neck blood sample from the autopsy, blood alcohol was 0.20 g/L. Analysis of the stomach contents revealed an ethyl alcohol level of 0.10 g/L. Investigation for substances classified as narcotics under French law was completely negative in all three media. Blood cyanide was within physiological concentrations at 54 ng/mL. Finally, blood GHB was normal, at 15.7 mg/L. Toxicology tests showed that blood concentrations following administration of prescribed doses were outside the usual therapeutic ranges. Clozapine was found in the neck and femoral blood and in the stomach contents, at concentrations of 480 ng/mL, 660 ng/mL and 1.8 mg/kg respectively. Cyamemazine was found in the neck and femoral blood and in the stomach contents, at concentrations of 480 ng/mL, 540 ng/mL and 6.5 mg/kg respectively. Caffeine was found in the femoral blood at a concentration of 260 ng/mL. Several xenobiotics were found in the hair, including zolpidem at a concentration of 1356 pg/mg, and cyamemazine at 221 pg/mg. There was not enough

hair to investigate for loxapine. Furthermore, zopiclone was not found in these samples. The forensic autopsy found no sign of trauma, and the conclusion was one of death by acute cardiorespiratory distress, with froth noted in the trachea and due to QT prolongation as it was reported that clozapine and cyamemazine at supratherapeutic concentrations can prolong QT interval (concenteration of clozapine was increased due to interaction with caffeine). The primary hypothesis was one of pulmonary edema, either medical (cardiac or pulmonary) or toxicological (medications, narcotics, or other toxins). The patient was also prescribed zopiclone (Imovane), alimemazine (theraline) for refractory schizophrenia and loxapine (loxapac) concomitantly for agitation. Patient had concurrent conditions of hyperglycemia with hepatic cytolysis and steatosis (liver disorder), morbid obesity, tachycardia, moderate uncomplicated cardiovascular atherosclerosis. No past medications were reported. Author commented that both medications (clozapine and cyamemazine) can cause sudden death, usually by prolongation of the QT interval as seen on the electrocardiogram in this patient.

Reviewer comment: *French causality assessment outcome is Uncertain. Considering compatible temporal relationship, the causal role of clozapine, and cyamemazine which are know perpetrators of the QT interval, are more likely to have caused the event than loxapine treatment. However the contributory role of loxapine cannot be excluded with the information at hand.*

Case 8: Case is on 61-year-old male patient, 170cm tall and weighing 75 kilograms. Concurrent conditions included right bundle-branch block and schizophrenia. The patient was a heavy smoker. Concomitant medications included loxapine, hydrochlorothiazide, macrogol for laxatives, amlodipine, candesartan cilexetil, betahistine, trimetazidine hydrochloride, celestamine and enoxaparin sodium. It was stated that the patient had normal electrocardiogram (ECG) 3 or 5 month ago (except for known right bundle branch block) with no prolonged QT intervals, normal blood electrolyte level and normal biological work-up. The patient was treated with risperidone long acting injection (LAI) (microspheres, intramuscular) at 50mg initiated on an unspecified date for about 2 years for schizophrenia. Concomitant medications included hydrochlorothiazide and laxatives. In early AUG-2011 the patient died from cardiac arrest. The patient was found on the ground near the cafeteria of hospital. In pharmacist opinion, the patient died from torasade de pointe (polymorphous ventricular tachycardia) but this information has not been confirmed. The French authorities considered cardiac arrest and QT prolonged as doubtfully related to treatment with risperidone, haloperidol and or to other co-suspect medications, according to French method of assessment. FR-EMA-20141111-kashyapprd-101500480

Reviewer comment: *In view of limited information presented in this case and concomitant multiple other drugs which may cause QT interval prolongation, the role of loxapine in the causality assessment for QT is Uncertain.*

Case 9: This spontaneous report was received from a physician via a company representative and concerns a 17-year-old male patient from France. The patient was treated with risperidone (oral) 6 mg. Other suspect drug included loxapine. On an

unspecified date, the patient experienced tachycardia and QT prolonged. As a corrective treatment, beta-blocking drugs were added. The dose of risperidone was decreased to 2 mg and loxapine was decreased to 50 mg. The patient recovered from tachycardia and QT prolonged on an unspecified date. The dose of risperidone was increased to 4 mg on unspecified date with no recurrence of adverse event.

Reviewer comment: *Case assessed using the French Method of causality assessment as Possible. The temporal association between the administration of loxapine and QT prolongation suggests some attribution. The negative rechallenge with risperidone adds to causality for loxapine. A synergistic adverse effect between risperidone and loxapine also cannot be excluded.*

Case 10: A male patient was administered a high dose of Solian (amisulpride) due to the use of Loxapine dropper by mistake. He presented a prolonged QT interval 10 min after the administration. No other event occurred in the next 24 hours. Due to the chronology of the events and the fact that the wrong dose concerns Solian only we consider the QT interval prolongation as not related to Loxapine but possibly related to Solian. However we do consider the medication error (error in medical device) as probably related to Loxapine and Solian. Due to the fact that the patient also had Loxapine the day of the event the contribution of Loxapine to the event cannot be excluded.

Reviewer comment: *Case assessed using the French Method of causality assessment as Unlikely. The drug was not administered and so cannot be linked to the ADR.*

Overall assessment using the Bradford-Hill criteria

Active substance	BH criterium	Assessment
Loxapine	Strength of association	5.22 PRR 10 ADR case reports 1 of which causality possible, 7 uncertain cases and 3 unlikely cases 3 articles directly relevant to QT effects in Pubmed.
	Biological Plausibility	Loxapine prolonged QT and blocked the human ether-a-go-go-related gene (hERG) channel, Ikr current in *in vitro* laboratory models at relatively high doses with an IC50 value of (1.8 μM). QTc prolongation was not seen in animal *in vivo* experiments.
	Biological gradient	Whether increased blockade of I_{Kr} occurs at increased doses was not investigated in preclinical or postmarketing data available to researcher.
	Experimental evidence and temporality	Of the 10 cases assessed, almost all had a temporal relationship between the events and the initiation of treatment however many cases were confounded by other drugs likely to cause QT prolongation or by underlying cardiac conditions. The QT/QTc study did not reveal significant effects after a single dose of loxapine 10 mg on cardiac repolarization as compared to placebo. Simairly QT prolongation was not seen in the repeat dose study by Cassella et al.
	Consistency	Reports originate from different countries in EU and non EU with possibly different prescribing patters. Most cases were uncertain or unlikely to be related with Loxapine. Most cases were confounded.
	Specificity	In preclinical data loxapine was found to bind the human ether-a-go-go-related gene (hERG) potassium channel, as well as affects AP duration which provides a plausible mechanism for QTc interval prolongation.
	Analogy	Other antipsychotics QTc interval-prolonging/arrhythmic drugs that also bind to hERG provided an analogy for loxapine causing QTc interval prolongation/arrhythmia.

Overall assessment	***In the Eudravigilance database the association was disproportionally reported for Loxapine over others and preclinical data demonstrates a mechanism of action. However literature and case review do not support causality of loxapine induced QT interval prolongation.***

Appendix 10:

Agomelatine

Agomelatine: VALDOXAN® 25 mg film-coated tablets

Mechanism of action: a new pharmacological mechanism of action for anti-depressants, which combines melatonin MT1 and MT2 agonist properties with a serotonin 5-HT2C antagonist effect.

Date EU approval: 19th February 2009

Indication: treatment of major depressive episodes

Availability in MT: Not available in government formulary list, available in private sector

Currently authorised SmPC wording:

4.2 Contraindications	Not listed
4.4 Warnings	Not listed
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

Preclinical data review:

In Agomelatine, 0.1 to 10µM, did not significantly inhibit the HERG channel tail current expressed in fibroblastic COS-7 cells. In isolated dogs cardiac Purkinje fibres, 10µM agomelatine caused a small decrease in the duration of the action potential without affecting the QT duration. At 1µM there was no appreciable effect. Effects of vehicle (DMSO) and of a blocker of HERG channels, E-4031 (10^{-7}M) were assessed independently. Agomelatine decreased HERG tail current density by 5%, 13%, and 21%, at 10^{-7}M, 10^{-6}M and 10^{-5}M, respectively but these effects were not significantly different from the spontaneous evolution of the HERG tail current density with time.

In vitro, agomelatine had no direct effect on human coronary arteries at 1µM but there was a small increase in KCl- and 5-HT-induced spasm. Doses up to 12.5mg/kg i.p. had almost no effect on blood pressure or heart rate in the pentobarbital-anaesthetized rat. Similarly, in the pentobarbital-anaesthetised cynomolgus monkey, agomelatine up to 8mg/kg i.v. had no significant effect on BP, heart rate, QTc or respiration. At 32mg/kg i.v. did lead to some increase in visceral vascular conductance.

A specific study of the effects of the drug on the ECG in unanaesthetized animals has not been conducted but, no effect on the ECG was observed in toxicological studies in awake or tranquilized cynomolgus monkeys treated intravenously or orally. In 12 healthy humans given single doses of 100 or 200mg of agomelatine in a crossover study and incorporating a placebo, agomelatine had no effect on QTc.

Reviewer's comment*: These results do not point toward an effect of Agomelatine on hERG current in in vitro studies or in vivo studies. There were no effects in the 12 health humans at single doses of 100 and 200mg. Preclinical data relating to hERG does not support a biological mechanism.*

Scientific literature review:

Donazzolo et al (2014) Evaluation of the effects of therapeutic and supratherapeutic doses of agomelatine on the QT/QTc interval: a phase I, randomized, double-blind, placebo-controlled and positive-controlled, crossover thorough QT/QTc study conducted in healthy volunteers

The effects of the antidepressant agomelatine up to a supratherapeutic dose (400 mg, single dose) on the QT corrected (QTc) interval were assessed in a randomized, double-blind, placebo- and positive-controlled, crossover thorough QT/QTc study in young healthy volunteers (29 males and 31 females). The primary criterion was the study of male or female population-derived QT-corrected interval (QTcP). The main analysis on the QTcP demonstrated that among the 10 post dose measurement times planned, the largest 1-sided 95% confidence interval upper bound of the difference between agomelatine 50 mg and placebo-adjusted means, and 1 of the differences between agomelatine 400 mg and placebo-adjusted means were both strictly inferior to the 10 millisecond upper-bound threshold of regulatory concern. The assay sensitivity was established with the positive control moxifloxacin (400 mg) and detected an effect on the mean QTcP interval that is around the threshold of regulatory concern (5 milliseconds). No relationship between QTcP and plasma concentrations of agomelatine was observed. In the authors conclusion, agomelatine up to 400 mg has no effect on the QTc interval as demonstrated in the present regulatory thorough QT/QTc study. (Donazzolo et al, 2014)

Reviewer's comment: *Agomelatine does not appear to cause QT interval prolongation in this study population. Of note is that the moxifloxacin effect, ie the effect of the positive control is just over the threshold of regulatory concern, ie 'around the treshold of regulatory concern 5ms.' Through QT/QTc studies may report up to 10ms lengthening with a 400mg dose of moxifloxacin. Therefore, the sensitivity of the assay to detect lengthening of the QT interval may be questionable and does not offer strong reassurance against the association of asenapine and QTc interval prolongation.*

Herrera-Comoglio (2013) Agomelatine and QT prolonged:

A report published in WHO pharmaceutical newsletter reporting that as of 25 January 2013, there were nine Individual Case Safety Reports (ICSRs) reporting the combination between agomelatine and QT prolonged in the WHO Global ICSR Database, VigiBase™. This possible association is not listed in the product information for agomelatine and only one published case report was found in a literature search. The ICSRs from VigiBase present cases in which agomelatine has been suspected as the cause of QT prolongation in patients with risk factors (female gender, congenital Long QT Syndrome), co- administration of other agents previously associated with QT prolongation, or intentional overdose. The analysis of these case reports suggests that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose. (Herrera-Comoglio, 2013)

Reviewer's comment: *This signal report presents cases which support the association of QT prolongation with Agomelatine. The author concludes that analysis of the ICSRs in the Vigibase database suggests that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose.*

Marx et al (2013) Neutrality of agomelatine on QT/QTc interval in healthy young volunteers: results from a randomised double-blind cross-over phase I study

Cross-over study in 56 healthy young volunteers (28 males and 28 females) exposed to single oral maximum therapeutic (50 mg) and supra-therapeutic (400 mg) doses of agomelatine, as well as to placebo and a single oral 400 mg dose of moxifloxacin as positive control. The exposure to agomelatine of 400 mg corresponds to the highest exposure obtained during drug interaction studies. The main analysis planned in the Study Completers Set (N = 56) on the primary criterion QTcP demonstrated that the 'thorough QT/QTc study' is negative. The largest 95% one-sided confidence interval upper bound associated to the comparison of agomelatine 50 mg to placebo was 5.57ms and the one associated to the comparison of agomelatine 400 mg to placebo was 8.24ms, strictly inferior to the 10ms upper bound threshold. The corresponding estimates of the difference between adjusted treatment means were 2.58ms and 4.70ms, respectively, below the 5ms mean effect threshold. The assay sensitivity was established with the positive control moxifloxacin. For most of the post-dose measurement times, i.e. 6 measurement times between 1.5 and 10 hours among the 10 planned, the estimate of the difference between moxifloxacin 400 mg and placebo adjusted means was between 5.69 and 9.24ms, above the 5ms mean effect threshold of regulatory concern. In conclusion, this 'thorough QT/QTc study', performed in accordance with the guideline ICH E14 in 56 completed healthy volunteers showed that agomelatine up to 400 mg did not significantly prolong QT/QTc interval. No clinically relevant prolonged QT/QTc interval is to be expected with agomelatine. (Marx et al, 2013)

Reviewer's comment: *Agomelatine was not found to cause QTc interval prolongation in this study. The assay sensitivities of the positive controls appear robust and offer reassurance against the association of agomelatine with QT prolongation.*

Kozian et al (2010) QTc prolongation during treatment with Agomelatine

A case report from the literature which concerns a female patient, treated with Agomelatine 25 mg daily during a hospitalization for depression. Previously she was treated with Duloxetine. Starting dosage of Duloxetine was 90 mg daily, then 60 mg daily and finally 30 mg daily due to nausea. At 30mg, Duloxetine was stopped for lack of efficacy. Concomitant treatment included local Fentanyl for lumboischialgia and Ramipril 10 mg daily for arterial hypertension. Following Duloxetine withdrawal, venlafaxin. treatment was started with a dose of 75 mg daily and increased to 300 mg daily. During the treatment with venlafaxine electrocardiogram QTc interval was prolonged (QTc correction method non specified, in females >470 ms abnormal, 450-470 ms borderline): 457 ms on the 4th day at a dose of 75 mg Venlafaxine daily and 449 ms on the 9th day at a dose of 150 mg Venlafaxine daily.After six weeks of treatment , Venlafaxine was stopped due to lack of efficacy. Before complete stop, agomelatine 25 mg daily was given concomitantly with Venlafaxine. After 10 days Agomelatine dose was increased to 50 mg daily. At this moment Venlafaxine was already withdrawn. During treatment with Agomelatine 50 mg daily Electrocardiogram QTc interval prolonged was found: -470 ms on the 17th day from Agomelatine initiation, the 7th day at Agomelatine 50 mg daily. -477 ms on the 31st day from Agomelatine initiation , the 21st day at Agomelatine 50 mg daily.

At a not specified date, Agomelatine dosage was reduced to 25 mg daily. Two days after dose reduction QTc interval was 463 ms. Seven days after dosage reduction, QTc was normalized at 455 ms. Agomelatine at a dose of 25 mg daily was ineffective and was withdrawn. Further

ECG controls were performed and QTc values were within normal ranges. (Kozian and Syrbe, 2010)

Reveiwers comment: *Case assessed using the French Method of causality assessment. Outcome Highly Probable due to positive temporality, no likely alternate explanation and a positive dechallenge.*

Post-marketing pharmacovigilance data review:

Case 1: 19-year-old female patient with a medical history of depression was treated with Agomelatine (25mg daily) and Duloxetine for depression. No concomitant treatment was reported. In early FEB-2016, the patient had an intentional overdose of 28 Agomelatine tablets (700mg) and 28 Duloxetine tablets and was admitted in emergency department. The ECG showed prolonged QT interval and the patient was hospitalized for monitoring. The patient was discharged from hospital the day after, reported outcome: recovered. AU-EMA-20160302-AUTODUP-458517

Reviewers comment: *Prolonged QT interval occurred in a patient following an overdose of Agomelatine and Duloxetine. The role of both drugs cannot be excluded. QT prolongation is not an expected adverse event with duloxetine. Outcome of causality assessment Probable.*

Case 2: The patient was a 52-year-old female was admitted to hospital due to suspicion of intentional overdose of Agomelatine. The emergency doctor found an empty blister for 14 tablets of Agomelatine. She consumed a relevant quantity of alcohol. She had blood alcohol at 1.77/ml. The patient stated that she took only two tablets Agomelatine (50 mg) because she wanted sleep well. At admission to the hospital the patient was somnolent and ECG showed prolonged QT time. DE-SERVIER-S11002379

Reviewers comment: *Outcome of causality assessment Probable due to positive temporality. An alternate explanation could be chronic alcoholism* (Campbell, 1993) *however there is no evidence in this case that the substantial alcohol content found in this patient was not a singular event but related to chronic alcoholism.*

Case 3: 28-year-old male with a medical history of depression and back pain. He was treated with Agomelatine (25 mg daily) for depression. Concomitant treatment included occasional intakes of Diclofenac for back pain. On 19-SEP-2011 at 11 pm, the patient attempted suicide by overdose: he took one pack of Agomelatine (28 tablets, 700 mg), one pack of Acetylsalicylic Acid and 30 tablets of Chlorprothixene. The morning after (20-SEP-2011), the patient himself called the emergency unit. At admission, he was somnolent and the ECG showed prolonged QT time (130%). Normal blood alcohol (0). The patient was monitored, no worsening of his general condition was noticed. On 21-SEP-2011 (8 am), QT time was normal. DE-SERVIER-S11007937

Reviewers comment: *Outcome of causality assessment using the French method is Uncertain for the role of agomelatine in the context of overdose of chlorprothixen. Chlorprothixen is a typical antipsychotic of the thioxanthene class which has a risk of malignant arrhythmias and is recommended for ECG monitoring prior to even starting treatment. The contribution of agomelatine cannot be excluded however.*

Case 4: concerns 55 year old female with a history of two previous suicide attempts. It was not specified whether the patient was treated with Agomelatine in the prior two reported events. On 22-OCT-2011, the patient attempted suicide by multiple drug overdose: 350 mg of Agomelatine, 3000 mg of Trimipramine, 150 mg of Zopiclone and

90 mg of Lorazepam. She was hospitalized but was only somnolent. However, later on her condition worsened, she lost consciousness and had to be intubated and ventilated. On 25-OCT-2011 at night, the patient was extubated but she is still somnolent, even more so because now she has been treated with sedatives. During the course, a QT prolongation was reported that normalized also in the night. Since the patient was still somnolent she could not give any information about the medication she took regularly prior to this suicide attempt. Even her husband could not give any information about this question. On 25th October she had recovered from loss of consciousness, and QT prolonged but her condition was still aggravated and she had not recovered from somnolence caused by the multiple drug overdose.DE-SERVIER-S11009314

Reviewers comment: *Outcome of causality assessment Uncertain in the context of overdose with trimipramine, which is known to prolong the QT interval at normal doses.*

Case 5: patient was a male in his mid-fifties with a medical history of depression, intermittent tachycardic atrial fibrillation with cardioversion in summer of 2012, arterial hypertension, hypertensive heart disease, hyperlipidemia and bronchial asthma. He had been treated since NOV-2012 with Agomelatine (25 mg daily) for depression. Concomitant treatment included Phenprocoumon (according to Quick time) for atrial fibrillation, Furosemide (40 mg daily) and Ramipril (5 mg daily) for arterial hypertension, Simvastatin (20 mg daily) for hyperlipidemia, Salmeterol / Fluticasone (4 puffs daily), Salbutamol (as needed) for bronchialasthma and Amiodarone since NOV-2012 for atrial fibrillation. In NOV-2012, an atrioventricular node ablation was performed, the patient received treatment with Amiodarone and QT prolongation developed. Amiodarone was stopped after several days and QT interval normalized. In the beginning of DEC-2012, ECG showed no QT prolongation.On 21-DEC-2012, a routine check-up showed again an ECG QTc prolongation of 530ms Outcome: Not Recovered. The reporter could not exclude a causal relationship to Agomelatine.DE-SERVIER-S13000026

Reviewers comment: *Outcome of causality assessment Unlikely as QT was first normal with agomelatine treatment alone, then aberrant following amiodarone treatment then normalized after stopping amiodarone and then prolonged. In this final episode of QT prolongation, the patient was not reported to be on Agomelatine and therefore the only contribution that agomelatine could have done was through a carry-over effect from November treatment which is unlikely. Any carryover effects would be more likely due to the amiodarone and its long half-life.*

Case 6: patient was a 39-year-old female patient with a medical history of a congenital long QT syndrome and depression for many years. Concomitant medication included Bisoprolol (2.5 mg daily), unchanged for years, due to the long QT syndrome. Due to a worsening of her depression, she was admitted to hospital on 02-NOV-2010. Agomelatine (25 mg daily) was initiated on 03-NOV-2010. On 02-NOV-2010, the admission ECG showed a QTc of 482 ms, heart frequency was 64 bpm. On 11-NOV-2010, the control ECG showed a prolongation of the QTc to 494 ms (heart frequency: 70 bpm). The patient was without symptoms. Agomelatine was stopped on 11-NOV-2010. The ECG performed on 15-NOV-2010 revealed an improvement of the QTc to

487 ms; the heart frequency was 63 bpm. On 19-NOV-2010 ECG, QTc was 485 ms, the heart frequency 68 bpm. DE-SERVIER-S10004951

Reviewers comment: *Outcome of causality assessment was Possible in this predisposed patient. However, the underlying disease could be an alternative explanation.*

Caae 7: The patient was a 35-year-old female with a medical history of borderline personality disorder. She had been treated for a long time with Agomelatine (25 mg daily) for borderline personality disorder. Concomitant treatment included Trimipramin (25 mg daily) for borderline personality disorder for a long time. The patient was treated for many years in outpatient psychiatric department. On 07-FEB-2013, the patient attempted a suicide by an intentional overdose intake of Agomelatine 25 mg (75 tablets, 1875 mg) and Trimpiramine 25 mg (50 tablets, 1250 mg) and was hospitalized in intensive care unit. At admission, the patient presented with hypothermia and mild QT-prolongation (no value provided). She was intubated and ventilated. During the psychiatric exploration, she told that she was sexually abused as a child. She heard that the man who abused her would move in the next door. Not knowing about the abuse, her parents invited the man for coffee. When the patient found out about this she lost her nerves, ran into the woods and took the pills. Previously, she had informed her friend about it, so that he came to look for her and found her. On 08-FEB-2013, the patient's condition was stabilized. She did not require ventilation anymore and her cardiorespiratory status was stable. On 12-FEB-2013, the patient was already well and discharged on 15-FEB-2013. Agomelatine was maintained. Outcome: Recovered for hypothermia, suicide attempt, and QT-prolongation. The psychiatrist was sure that the suicide attempt was definitely not an adverse reaction of Agomelatine, since the patient had been treated without any problems for a longer time and never had suicidal ideation. It was an emotional over-reaction under extreme psychic stress. Hypothermia was also not a reaction on Agomelatine but caused by exposure to the cold in the woods. DE-SERVIER-S13000930

Reviewers comment: *Outcome of causality assessment Uncertain. In the context of a massive overdose of agomelatine and trimipramine, a drug expected to cause QT prolongation and TdP in some patients.*

Case 8: report refers to a 38-year-old female patient. The medical history included Crohn's disease (not active since 2002) and one suicidal attempt with venlafaxine and diazepam in Mar 2011. The patient's current conditions included genital haemorrhage and depression treated with Agomelatine 25 mg film coated daily from Oct 2011to Nov 2011. On an unspecified date, probably by the end of Nov 2011, the patient attempted suicide by swallowing 14 tablets of Agomelatine 25mg (agomelatine) 350 mg and 20 tablets of Diazepam 150mg (3000mg) among other substances such as Bupropion. She was found at home 4 hours later, in a drowsy state. She had an epileptic fit at home. She was admitted to intensive care unit where she also had a short epileptic fit, which resolved after 30 seconds. She was still drowsy and disoriented. BP was 110/40mmHg, heart rate: 110 bpm. EMV (eye, motor, verbal) score 4-6-4 and pupils were dilated and slowly responsive. She remained stable and somewhat disoriented with retrograde

amnesia, possibly due to multi drug overdose, the effect of Diazepam or related to a post-ictal effect. A prolonged QT at 504ms has reported. Propofol was administered for a few hours to prevent new fits. On Nov 2011, Agomelatine and diazepam were withdrawn. On 01 Dec 2011,liver tests were normal. After one day she was transferred to the psychiatry unit, and eventually discharged after two weeks and a half. The outcome of the events reported as recovered complete recovery. The epileptic insults and the prolonged QT were possibly attributed to Agomelatine. NL-EMA-20120911-AUTODUP-285158

Reviewers comment: *Outcome of causality assessment Uncertain as bupropion has a listed effect of QTc prolongation in the context of overdose.*

Case 9: concerns 48-year-old female with a medical history of loss of right eye following an accident in childhood and burn-out-syndrome in 2011 (resulting in work disability from 2011 to 2012). She had financial problems for a long time. She was treated since an unspecified date with Agomelatine On 11-FEB-2013, following a discussion with her bank, the patient had an intentional intake of Agomelatine (6 tablets, 150 mg) and Mirtazipine (6 tablets), concomitantly with a bottle of wine, with suicidal intention. She was admitted to hospital on the same day. At admission, the patient presented with nervousness, tremor, reduced sleep, narrowing of thoughts with a tendency to ruminate and depressed mood, with emotional depletion, hopelessness, slight anxiety and inner restlessness. Lab tests showed blood sodium 135 mmol/L, glomerular filtration rate 80.2 ml/min,blood glucose 122 mg/dl, ALT 36 U/L, GGT 46 U/L, triglycerides 392 mg/dL and cholesterol 273 mg/dL. ECG performed at admission showed a QT prolongation of 448 ms, which went back to normal on 12-FEB-2013 (411 ms). The patient decided to leave the hospital on 12-FEB-2013. She was free of complaints. An adjustement disorder, in a context of difficult social and financial situation, was eventually diagnosed. The patient was lost to follow-up The reporter assessed the QT prolongation as related to Mirtazapine (not related to Agomelatine) DE-SERVIER-S13001123

Reviewers comment: *Outcome of causality assessment is Probable. QT interval prolongation is not a listed effect with mirtazepine in the EU.*

Case 10: A 76-year-old woman developed QT prolongation 8 days after starting agomelatine 25mg and escitalopram 5mg. Other reported ADRs included grand mal convulsions, vomiting and constipation. She died 16 days after starting agomelatine and escitalopram. The medical history of the patient was not specified. The patient's concomitant medication included lansoprazole; hydrochlorothiazide, irbesartan(150mg). AR-TEVA-436548ISR

Reviewers comment: *Outcome of causality assessment Uncertain as escitalopram has a known effect of QTc prolongation at therapeutic doses.*

Case 11: concerns female patient treated with agomleatine. Concomitant treatment included Valsartan and Hydrochlorothiazide. On an unspecified date, ECG showed prolonged QT interval. No value was provided. Agomelatine was maintained. On an

unspecified date, a further ECG control showed a normal QT value. The senior physician reported there was no causal relationship to agomelatine. DE-SERVIER-S13008553

Reviewers comment: *Outcome of causality assessment Unlikely as adverse event resolved while patient was still on the drug.*

Case 12: 32-year-old female patient attempted overdose by ingestions of ziprasidone, pregabalin, lamotrigine, agomelatine, ibuprofen, and venlafaxine. The woman developed QT prolongation 1 day after an intentional and fell into a coma. She was reported to have recovered after 2 days. Causality: possibly related to all suspected drugs. AR-EMA-20140116-raevhumanwt-143522574

Reviewers comment: *Outcome of causality assessment Uncertain as other drugs such as Ziprasidone are more likely to have caused the event.*

Case 13: concerns the occurrence of prolonged QT in a 58-year-old female patient was started on venlafaxine 75mg and developed borderline QT prolongation, which later normalised. Agomelatine 25mg was added to her regimen. Venlafaxine was discontinued due to lack of efficacy, and the dose of agomelatine was increased to 50mg. She developed QT prolongation 17 days after starting agomelatine. She had a QTc interval of 477ms on day 31. The dose of agomelatine was reduced, and her QTc interval normalised 7 days later. At the time of reporting, the event was resolved. AR-GlaxoSmithKline-B0961270A

Reviewers comment: *Outcome of causality assessment Probable due to temporality, agomelatine being the only suspect drug and a positive dechallenge.*

Case 14: Coma on voluntary drug intoxication. The patient was found on the ground, with a Glasgow coma scale 3. A Narcan was performed without success (Narcan Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression). The following drugs were found next to the patient: Ibuprofen, Zolmitriptan, Seroquel, Olanzapine, Thalene, Zopiclone, Tetrazepam and Agomelatine. On the neurological level, the patient was in a calm coma, glasgow scale 3. No disorders of atrioventricular or intraventricular conduction. Corrected QT was elongated at 513 ms. The treatment undertaken includes antibiotic therapy with Augmentin in the context of mechanical ventilation and gradual warming. Secondarily, the patient becomes hypotensive, initially responding to filling, and then requiring the introduction of noradrenaline. The ECG at 3h finds an elongated QT but which is shortened in comparison to that of admission. At around 6 am, the patient presented with tachycardia 150 bpm, and a restless awakening. The QT normalizes, the patient remains slightly tachycardia. The patient was extubated but be confusion and visual hallucinations remained. FR-AFSSAPS-ST20140240

Reviewers comment: *Outcome of causality assessment Uncertain as other drugs such as Seroquel are more likely to have caused the event.*

Case 15: concerns a 46-year-old female with a medical history of depression, borderline disorder, arterial hypertension, a triple osteotomy of right hip and valgising interochanteric osteotomy due to dysplasia on both sides. In November-2012 she had suffered from a cerebral seizure due to discontinuation of a benzodiazepine medication and in August-2013, she had severe obesity (BMI = 34.9). This patient was being treated with agomelatine, lamotrigine and metoprolol. On 20-MAR-2014, the patient called the emergency room after a suicidal attempt with Agomelatine 125 mg, lamotrigine 500 mg, metoprolol 500 mg and the cold and flue Medicine MediNait 200ml. The patient reported that after intake of the cold medicine MediNait she had vomited almost the whole amount. No evidence of current triggering factors. At admission the patient was awake, sleepy but fully oriented. She had mydrasis, isochoric pupils with prompt light reaction. Lungs were free without rales, heart clear and rhythmic, pronounced hypotension with an initial blood pressure of 70/45 mmHg, bradycardia of about 50/min. No leg oedmas. Neurologic examination did not show paresis, no sensitivity disturbances. Oxygen saturation at admission was at 89%, in the further course no remarkable values. Laboratory tests showed pathologic values for creatinine 1.3 mg/dl, urea 19 mg/dl, erythrocytes 4.18/pl, Hb 11.7 g/dl, hematocrit 35.4 %, PTT (partial thromboplastin time) 27 sec (no reference values reported). ECG from 20-MAR-2014 documented a bradycardia 52/min with sinus rhythm. Normal position of the heart, QT time 462 msec, T negativations in III, V1-V4. No specific treatment was recommended due to stable circulatory condition and because the intake time was more than 6 hours ago. Blood pressure and heart rate normalized successively. On 21-MAR-2014, in the morning the patient was awake, fully oriented and had stable blood circulation. The follow-up ECG on 21-MAR-2014 showed a normal frequent sinus rhythm with 72/min and a persisting T negativation in V1-V5 with unchanged QT time. On 21-MAR-2014 the patient was in good general condition, without further medication to the psychiatric ward (in-patient treatment). Outcome Recovered. The reporter assessed the event as not related to Agomelatine but related to her medical history. DE-SERVIER-S1400169

Reviewers comment: *Outcome of causality assessment Probable. The other drugs taken in overdose are not known to cause QT prolongation although Lamotrigine has blocked hERG dose dependently in preclinical studies.*

Case 16: This is a consumer report from Germany. Patient was a 45-year-old female with a medical history of migraine for 30 years , surgery in 2007 due to endometriosis, depression, anxiety disorder and a severe sleep disorder. In 2006, due to a difficult family situation and pain caused by migraine and endometriosis, she started taking medicines and she became drug dependent. She had been treated with agomelatine 25 mg daily for depression and drug deprivation since 20-DEC-2010. Concomitant treatments included for sleep disorder taken mainly at night since 2006 (she could not sleep): Zolpidem (80 mg daily), Diazepam (60 mg daily) and Lorazepam (6 mg daily) also for depression. She had taken also Codeine/Paracetamol (10 tablets daily) for pain, on which she became dependant. On 21-DEC-2010, the patient suffered from a severe

migraine attack .On 22-DEC-2010, she experienced diarrhoea, On 23-DEC-2010, she experienced dizziness (only this day) and she also reported that she could not sleep all the time. Agomelatine was discontinued at the patients initiative. On 10-JAN-2011, her doctor recommended that she should continue Agomelatine then she again took one tablet of it. There were no side effects but she could not sleep at all. The patient was very afraid of becoming dependent of any new medicine. On 18-JAN-2011, the patients psychiatrist was contacted and explained that the patient suffered from a borderline personality disturbance and severe depression. She was always very sensitive regarding the side effects which were written in the patient's information leaflet. Therefore the complaints which were reported by the patient should be assessed very carefully. The symptoms could be interpreted also with the underlying disease. The patient could not sleep in the night after taking Agomelatine because she took the other drugs which she always use maybe too late. The psychiatrist assessed the complaints as not directly related to Agomelatine and Agomelatine was maintained.

In OCT-2011, Quetiapine (600mg daily) was added for premedication of planned hospitalisation for drug withdrawal. Mid-NOV-2011, the patient visited an Internist. A prolonged QT time was found and the internist decided to stop Agomelatine and Quetiapine. On 22-NOV-2011, the patient was hospitalized for the planned withdrawal treatment. During hospitalisation, ECG was normal (no QT prolongation). The patient was treated with occasional intakes of Pregabalin (300mg), Pipamperone and Metamizole for restlessness and insomnia. On 04-JAN-2012, the drug withdrawal was successful and the patient was discharged. According to the psychiatrist, the QT prolongation was caused by Quetiapine 600mg as pre medication (known adverse reaction) and not by Agomelatine. DE-EMA-20140903-deeptisp-154719857

Reviewers comment: *Outcome of causality assessment Uncertain as other drugs such as Quetiapine are more likely to have caused the event.*

Case 17: concerns a 49-year-old female with a medical history of ECG abnormality since childhood, family history of cardiac disorder and QTc prolongation diagnosed on 28-MAY-2014. On 27-MAY-2014, she had been admitted to a psychiatric hospital (unspecified reason) and QTc prolongation (478ms) was diagnosed during hospitalization. The patient was treated with Trimipramine (25 mg daily) from 27-MAR-2014 to middle JUN-2014 and Venlafaxine (75 mg daily) since the beginning of 2014, on 10-APR-2014 the dose of Venlafaxine was increased to 150mg daily, then stopped in the middle of JUN-2014. Agomelatine (25 mg daily) and Promethazine (occasional intakes of 25 mg) were started in the second half of JUN-2014. Prior to Agomelatine initiation the patient experienced QTc prolongation: on 02-JUN-2014-472 ms, on 06-JUN-2014 - 482 ms and 499 ms on 12-JUN-2014. Promethazine was stopped by the patient herself in AUG-2014. In the beginning of AUG-2014, Duloxetine was started and then eventually stopped after two weeks due to nausea. The patient immediately recovered from nausea after Duloxetine withdrawal. On 15-SEP-2014, ECG showed QTc prolongation of 474 ms. No aggravation of QT prolongation during the treatment with Agomelatine was observed. Agomelatine was maintained. On 23-SEP-2014, the reporter assessed QTc prolongation as definitely not related to Agomelatine but as pre-existing and stable condition. DE-SERVIER-S14006165

Reviewers comment: *The patient had QT prolongation prior to Agomelatine initiation, no aggravation during the treatment was observed. This case is assessed as Unlikely by the French method of causality.*

Case 18: case was received from a consumer in Italy concerning a 79-year-old male with a medical history of atrial flutter (since 2000 and in 2006), atrioventricular node ablation (in 2005 and 2006) requiring pacemaker implantation (in 2006), prolonged QT interval (480 - 486msec) since an unspecified date, lower limb neuropathy and multiple myeloma since 2000. No family history of long QT syndrome. He has been treated with Agomelatine (25 mg daily) since 2013 for depression. Concomitant treatments included Warfarin since 2006, Sotalol (240 mg daily) since 2006, Alprazolam, Lormetazepam since 2013 and Pregabalin (250 mg daily) since MAR-2014. Previous treatment included Thalidomide (unspecified dose) from 2008 to DEC-2013. On approximately 15-APR-2014, Agomelatine was stopped (for non medical reason) and restarted approximately on 15-MAY-2014. On 17-MAY-2014, Warfarin was stopped and Rivaroxaban (20 mg daily) started. On 27-MAY-2014, ECG showed a worsening of the QT interval prolongation (QTc 501 msec). On 08-JUL-2014, ECG showed a QTc prolongation at 506 msec. Pregabalin was reduced from 250 mg daily to 150 mg daily. On 16-JUL-2015, Agomelatine was stopped for non-medical reason and replaced by Paroxetine. On 18-JUL-2014, ECG showed a QTc prolongation of 496 msec. Pregabalin was increased up to 175 mg daily. On 27-JUL-2015, the patient decided to re-introduce Agomelatine. IT-MINISAL02-320994

Reviewers comment: *The role of Agomelatine in the occurence of QT prolongation is Unlikely. This event could be an natural evolution of the patient's medical history of QT prolongation.*

Active substance	BH criterium	Assessment
Agomelatine	Strength of association	18 ADR Case reports, 2.51 PRR, Pubmed literature search yielded 3 articles referring to QT effects including 1 literature case report. 1 conference abstract was retrieved from a search from other sources.
	Biological Plausibility	Agomelatine did not prolong QT or significantly block the hERG channel, Ikr current in *in vitro* or *in vivo* laboratory models. A small decrease in the action potential due to agomelatine was observed. If agomelatine had an effect on QT it would not be through a direct inhibition of hERG.
	Biological gradient	Increased blockade of I_{Kr} at increased dose was not observed in studies. In post marketing data, very high doses of agomelatine in overdose did not lead to greater prolongation of the QT interval.
	Experimental evidence and temporality	The two randomised and controlled clinical studies in healthy volunteers, did not show any evidence of QT prolongation. However from the postmarketing data available, in 14 out of 18 temporally related cases a contribution of agomelatine to QT interval prolongation could not be excluded. In 1 literature case, agomelatine was the only drug being given and dechallenge was positive. In 5 cases agomelatine appeared likely (probable outcome) to be the cause of the QT interval prolongation as although agomelatine was taken in overdose with other drugs, these drugs are not expected to prolong the QT. In 1 case, agomelatine possibly prolonged the QT interval but an underlying stabilised LQT syndrome was present in that patient. These 7 (1+5+1) cases form the strongest base of evidence for the association of agomelatine with QT prolongation. In a further 8 cases, the involvement of agomelatine was uncertain but could not be excluded. A positive temporality was present, however the presence of other drugs known to prolong QT or the presence of relevant underlying disease were important confounding factors which impeded the attribution of agomelatine to drug induced QT prolongation. Finally, a signal report published in the WHO newsletter concluded that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose.
	Consistency	Both healthcare professionals and patients have reported the

		same event. Reports originate from different countries in the EU and non EU with possibly different prescribing patters.
	Specificity	Agomelatine was not found to bind the human ether-a-go-go-related gene (HERG) potassium channel, which would provide a plausible mechanism for QTc interval prolongation/arrhythmia.
	Analogy	Agomelatine has a novel mode of action which is markedly different from other antidepressants. No analogy can be drawn in this case.
Overall assessment	*In favour of the association, the most compelling evidence comes from the 14 post marketing cases (1 highly probable, 5 probable,1 possible and 7 uncertain) as well as the signal report of 2013 published on the WHO pharmaceutical news letter which concluded that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose.* *The post marketing data assessed here does not go against this conclusion. In 10 /18 cases reviewed, the patient had attempted suicide by overdose as an unfortunate but common occurrence in patients treated for MDD . In 15 of these cases an underlying predisposition to cardiac disease could not be excluded.* *Indeed, the indication for which agomelatine is being described, that is, the treatment of major depressive disorder, is highly prevalent in cardiac patients. An epidemiological review by Huffman et al, reports the prevalence of Major Depressive Disorder (MDD) to be between 31–45% for patients with coronary artery disease or undergoing coronary artery bypass graft (CABG) surgery out of which 15–20% had the full syndrome of MDD. This rate of MDD is roughly threefold higher than in the general population. Similarly, a meta-analysis of patients with heart failure found prevalence rates of 36% for increased depressive symptoms and 20% for MDD.* (Huffman et al, 2013) *Against the association is the preclinical data as well as the 2 placebo controlled clinical trials in healthy volunteers which did not show any effects of QT prolongation by agomelatine in vitro or in vivo.* *Although a plausible biological mechanism via hERG inhibition cannot be established, in line with conclusions published in the WHO report, the overall conclusions from this assessment is that prolongation of the QT interval by agomelatine cannot be excluded, especially in patients with predisposing risk and in overdose. Nonetheless, the incidence of such events are rare considering the widespread use of this antidepressant.* *Based on this assessment, a change to the SmPC in sections could be warranted in sections 4.4, 4.5 and 4.8. A recommendation for a baseline ECG prior to commencement of therapy with agomelatine could be warranted at the very least in those patients already being treated for cardiac conditions.*	

Appendix 11:

Prucalopride

Prucalopride: Resolor® 1mg and 2mg film-coated tablets

Mechanism of action: a novel agent that stimulates gastrointestinal (GI) motility and acts primarily on different parts of the lower GI tract (enterokinetic).

Date EU approval: 15th October 2009

Indication: Treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.

Availability in MT: not available on the GFL

Currently authorised SmPC wording:

Section	Wording
4.3 Contraindications	*Not listed*
4.4 Warnings	*Not listed*
4.5 Interactions	*Not listed*
4.8 List of ADRs	*Not listed*
5.0 Pharmacology	*Not listed*

Number of reports in Eudravigilance database: 3 total, 1 not assessable, 1 EU, 1 Non-EU.

Statistics (PRR, CHI^2):

1.4633894	4.5089675	13.8929445	8.210713184

Summary of company preclinical data

In Vitro Cardiovascular Studies

An extensive programme of cardiovascular safety studies was undertaken with prucalopride in various animal species, at concentrations covering and exceeding the plasma concentrations of prucalopride that are reached after therapeutic doses in man (20 nM).

Prucalopride was evaluated in a range of isolated cells and cardiac tissues under various experimental conditions (e.g. normal, hypokalaemia, bradycardia and tachycardia), including human embryonic kidney cells (HEK293) and monkey kidney cells (COS-7) transfected withthe human ether-a-go-go-related gene- encoded potassium channel (hERG), ventricular myocytes isolated from guinea pig hearts, Purkinje fibers of rabbit and canine hearts, papillary muscles of guinea pig hearts and isolated rabbit heart preparations. In addition, the effects of prucalopride on the electrophysiological changes induced by ketoconazole, terfenadine and erythromycin in hERG-transfected HEK cells and isolated rabbit hearts were evaluated.

Prucalopride has no effect on the IKr current at concentrations up to 1 μM (370 ng/ml; approximately 49-fold higher than the Cmax after a therapeutic dose in man). At very high concentrations (exceeding 1 μM), prucalopride concentration-dependently attenuates the rapidly activating component of the delayed rectifier potassium current IKr in hERG-transfected HEK cells and in ventricular myocytes of guinea pig hearts. The EC50 for IKr inhibition in hERG-HEK cells in the five studies varied between 4.1 to 22 μM (i.e. between 200-fold and 1100-fold higher than the Cmax at the therapeutic dosage in man). The EC50 for IKr inhibition in ventricular myocytes (guinea pig heart) was in the same range i.e. 10 μM (3700 ng/ml; approximately 490-fold higher than the Cmax at the therapeutic dosage in man). This clearly dissociates prucalopride from the non-selective 5-HT4 receptor agonist cisapride, with a concentration ratio ≤5 between its 5-HT4 receptor-mediated effects and its inhibitory effect on the IKr current. Prucalopride also had little or no effect on other membrane ion currents such as IK1, IKs, INa or ICa,L at concentrations far (490-fold) exceeding therapeutic plasma levels.

Also in tissue preparations, at high concentrations only (≥3x10-6 M, 1110 ng/ml, 150 times the Cmax at the therapeutic dosage in man), prucalopride modestly prolonged the duration of the action potential in isolated guinea pig papillary muscles, canine and rabbit Purkinje fibres and in isolated rabbit hearts (APD90 +14% to +22%).

There were no additive effects of prucalopride on the electrophysiological changes induced by ketoconazole, terfenadine and erythromycin.

In Vivo Cardiovascular Studies

The standard ECG intervals including the duration of the intervals PQ, QRS, QT and QTcB, QTcF of the ECG, ECG morphology (presence of P waves, association between PQ and a normal QRS complex, absence of atrioventricular blocks, ventricular premature beats, tachycardia or fibrillation), blood pressures, LV contractility and relaxation, cardiac output and stroke volume, have been evaluated in a range of conscious and anaesthetised animals treated with single and / or repeated high doses of prucalopride during experiments on cardiovascular safety pharmacology or toxicology.

In animals such as guinea pigs and rabbits only very high i.v. doses (≥1.25 mg/kg) of prucalopride prolonged the duration of the QTcB interval, as expected. In these animals, the IKr component of the delayed rectifier potassium current is dominant over other membrane ion currents such as IKs or Ito in modulating the duration of the repolarisation phase of the action potential.

In dogs high doses of prucalopride had no relevant effect on ECG- intervals including PQ, QRS and the duration of the QT interval corrected for heart rate according to Bazett (QTcB) and Fridericia (QTcF), as well as on the duration and normal course of the monophasic action potential at the endocardial site of the right ventricle. In conscious dogs, after intravenous dosing or at high oral doses, a slight and transient increase in systolic and diastolic blood pressure was induced with some concomitant effects on heart rate at higher doses, without effect on ECG characteristics. Since 5-HT4 receptors are not expressed in canine cardiac tissue and since similar effects were absent in anaesthetised animals, the experimental conditions of restraint together with a pronounced effect on gastrointestinal motility, known to occur at these doses, might have contributed to the observed effects. In addition, no apparent effects of prucalopride on ECG characteristics were reported in conscious dogs in the repeated dose toxicity studies of up to 12 months duration.

In anaesthetised juvenile pigs, a slight and transient increase in heart rate and systolic and diastolic blood pressure was noted from an i.v. dose of 0.02 mg/kg upwards (plasma level 6.7 ng/ml). The maximal effect was seen at 0.16 mg/kg (plasma level 70-80 ng/ml), approximately 9-fold higher than the Cmax after a therapeutic dose in man. This dose resulted in a transient increase in heart rate of 14 beats/min, and an increase in systolic and diastolic blood pressure of 1.4 and 1.9 kPa, respectively. The response faded gradually over a 30 minute interval. Higher doses administered subsequently, were less effective. This observation together with data on 5-HT4 receptor-mediated responses on porcine and human atrial tissues might explain the transient and limited increase in heart (6 beats/min) rate observed in volunteers upon first exposure to the compound. Prucalopride up to the highest dose tested (1.25 mg/kg i.v., plasma level 757 ng/ml) did not affect systolic and diastolic pulmonary artery pressure, LV end-diastolic pressure, LV contraction and relaxation, cardiac output, stroke volume, and systemic and pulmonary vascular resistance, the duration of the PQ interval, the QRS complex, the QT, QTcB and QTcF intervals of the ECG. No aberrant ECG complexes such as irregular RR interval, supraventricular arrhythmias, ventricular premature beats, ventricular tachycardia and ventricular fibrillation occurred during the course of the experiments, and normal P-wave generation was observed in all animals that were given prucalopride up to 1.25 mg/kg.

Moreover, in a classical model for drug-induced pro-arrhythmogenesis (anaesthetised, methoxamine-challenged rabbits), neither the morphology nor the homogeneity of the QT duration, as measured in several leads of the surface ECG (QT dispersion) is changed by prucalopride. Following intravenous administration, prucalopride failed to elicit polymorphic ventricular tachycardia or Torsades de pointes or other cardiac arrhythmias (at up to 20 mg/kg or 4812 ng/ml or 1.3x10-5M, approximately 642-fold higher than the clinical plasma levels).

Reviewer conclusions: *Prucalopride induced a transient increase in heart rate and a concomitant change in blood pressure in anaesthetised pigs. hERG inhibition in human*

embryonic kidney cells (HEK293)and Action Potential duration prolongation in perfused tissues were seen at very high doses not expected to occur in man.

Summary of company clinical data

Cardiovascular Safety Studies in Healthy Volunteers and Frail Elderly Patients

Two healthy volunteers studies were conducted to evaluate the effects on ECG parameters of prucalopride doses up to supratherapeutic doses of 10 mg and 20 mg o.d., respectively. The design of these studies is aligned with the CPMP guidelines for the study of QTc except for the lack of a comparator arm. This specific requirement was not included in the guidelines at the time that the studies were performed.

A thorough QT/QTc study (according to ICH E14) was performed after the submission of the original MAA on 22 April 2008 to confirm the absence of a QT prolongation effect with prucalopride treatment. The only finding in these studies was a slight increase in heart rate.

With one exception (at the supratherapeutic dose of 20 mg), at none of the time-points the mean difference for QTcF exceeded +5 ms, including the treatment period from Day 1 (2 mg) up to Days 10-13 (20 mg). On Days 10 to 13, the dose was fixed at 20 mg (i.e. 10 times the therapeutic dose). On Day 13 at 2 hours postdose, the mean within-patient difference for QTcF between prucalopride and placebo treatments exceeded 5 ms (+5.4 ms; 2-sided 95% CI: -1.4; +12.2; the upper limit 1-sided 95% CI was +11.1 msec). This is also the only time-point where the upper limit of the 95% CI exceeded 10 ms. The extremes of the time-matched differences at individual time-points are evenly distributed around zero. None of the individual differences exceeded 60 ms and the largest individual increase is 49 ms, occurring on Day 0, predose. Over time, or with increasing dose, no increase in mean difference was observed. There was also no apparent correlation between QTcF and prucalopride plasma concentrations.

A prolonged QTcB, QTcF or QTlc interval was noted if the interval was >450 ms for men or >470 ms for women. A borderline QTcB, QTcF or QTlc interval was said to occur in case the interval was between 430-450 ms in men, and between 450-470 ms in women. No QTcF, QTcB, or QTlc values >500 ms were demonstrated and none of the subjects had a prolonged postbaseline QTcF, QTcB, or QTlc interval. Also, no subjects with postbaseline borderline QTcF or QTlc were observed.

During prucalopride treatment, none of the corrected QT intervals showed increases vs. baseline above 60 ms compared with 1 subject in the placebo group. A similar number of increases in QTcB, QTcF and QTlc values between 30-60 ms vs. baseline was observed during the prucalopride and placebo treatment periods. Holter monitorings (24 hours) were performed at baseline (Day 0) and on Day 13, to detect any possible occurrence of arrhythmias. Findings were considered normal, except for 1 subject on Day 13 of prucalopride treatment. However, the abnormality was not specified and not considered clinically relevant.

After the submission of the MAA on 22 April 2008, the company (Movetis) performed a double-blind, randomised, placebo- and positive-controlled thorough QT/QTc study according to ICH E14. The results from this study showed that prucalopride, at therapeutic

and supratherapeutic doses of 2 and 10 mg daily, respectively, had no statistically significant and clinically relevant effect on cardiac repolarisation based on procedures described in ICH E14. A single oral dose of 400 mg moxifloxacin was included as a positive control. No subject has a QTcSS increase of >60 msec that resulted in QTcSS > 500 msec, the parameter of usual regulatory concern. At 2 mg, an increase in HR was seen, which was similar to the increase at 10 mg dose. No significant differences were seen between prucalopride and placebo in ECG morphologic changes or arrhythmias and observed abnormalities were not considered to be of clinical relevance.

Absence of any clinically significant effect of prucalopride on cardiac repolarisation was confirmed: for both the therapeutic prucalopride dose of 2 mg and for the supratherapeutic dose of 10 mg, the mean differences in time-matched QTcSS change from baseline between prucalopride and placebo were all. There were no QTcSS outlying values > 450 msec at any timepoint, and no subject had an increase of >60 msec that resulted in QTcSS >500 msec.

A small increase in heart rate relative to placebo was observed but this did not exceed 6 bpm at any timepoint.

In conclusion, the data from the 2 Phase I studies that were specifically designed to evaluate the effect of prucalopride on cardiovascular safety parameters showed that, apart from a slight increase in heart rate, there were no differences between prucalopride and placebo on the measured cardiovascular parameters. No prolonged QTc intervals or increases in QTc above 60 ms vs. baseline were observed.

The results from the thorough QT/QTc study according to ICH E14 confirm the lack of QT prolongation with prucalopride. There were no significant differences between prucalopride and placebo at therapeutic (2 mg) and supratherapeutic doses (10 mg), based on mean QT measurements and outlier analysis. The absence of a PK/PD correlation confirms the lack of QT prolonging effect of prucalopride.

Additional important data are provided by another company study, a randomised, double-blind, dose-escalation safety study with extensive ECG assessments including Holter monitoring in frail elderly constipated patients who were living in a nursing facility. The mean age of the patients was 83 years, and approximately 80% of these patients had a history of cardiovascular disease. Patients were treated with prucalopride 0.5 mg, 1 mg or 2 mg o.d. during 4 weeks. ECG measurements showed an increase in median heart rate 3 hours after treatment administration in both the placebo and the prucalopride groups. No relevant differences between active and placebo treatment were noted, and no dose relationship was observed. No consistent or clinically relevant treatment-related differences were noted in PR, QT, QTcB, QTcF, QTlc or QTdisp time intervals. Additionally, there were no events of sustained ventricular tachycardia, ventricular fibrillation, syncope or torsade de pointes in this frail elderly population.

Reviewers conclusions: *The four specific cardiovascular safety studies presented by the company provide reassurance that prucalopride treatment has no adverse effect on QT.*

Scientific literature

Shin (2016) Patient considerations in the management of chronic constipation: focus on prucalopride.

Chronic constipation is a common condition that significantly impacts health care utilization, productivity, and quality of life. Laxatives are commonly used, although often insufficient in restoring normal bowel function or providing adequate relief. There remains a significant need for the development of novel agents to optimize treatment of this condition. This review provides an overview of the preclinical and clinical trial data, supporting the efficacy and safety of prucalopride, a highly selective 5-HT4 receptor agonist that has been approved by the European Medicine Agency for the treatment of chronic constipation in adults who have failed standard laxative therapy. Unlike older 5-HT4 agonists, prucalopride has not been associated with adverse cardiovascular side effects or QT prolongation owing to its high selectivity and affinity for the 5-HT4 receptor without clinically significant cross-reactivity at the human ether-à-go-go-related gene (hERG) potassium channel or 5-HT receptor subtypes that have previously been implicated in adverse cardiovascular events and arrhythmias. Careful safety assessments have documented the relative safety and tolerability of this agent in various patient groups. Focus has also been placed on demonstrating efficacy with regard to bowel function, symptoms, and patient-reported outcomes such as the Patient Assessment of Constipation-Symptoms and the Patient Assessment of Constipation Quality of Life scores to support the use of prucalopride as a safe and effective therapeutic option for the management of chronic constipation. (Shin, 2016)

Reviewer conclusions: *This publication provides reassurance on the safety of prucalopride and the abscence of any correlation with QT interval prolongation.*

Tack et al (2012) Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders.

The nonselective 5-HT(4) receptor agonists, cisapride and tegaserod have been associated with cardiovascular adverse events (AEs). Objective To perform a systematic review of the safety profile, particularly cardiovascular, of 5-HT(4) agonists developed for gastrointestinal disorders, and a nonsystematic summary of their pharmacology and clinical efficacy. Method: Articles reporting data on cisapride, clebopride, prucalopride, mosapride, renzapride, tegaserod, TD-5108 (velusetrag) and ATI-7505 (naronapride) were identified through a systematic search of the Cochrane Library, Medline, Embase and Toxfile. Abstracts from UEGW 2006-2008 and DDW 2008-2010 were searched for these drug names, and pharmaceutical companies approached to provide unpublished data. Results: Retrieved articles on pharmacokinetics, human pharmacodynamics and clinical data with these 5-HT(4) agonists, are reviewed and summarised nonsystematically. Articles relating to cardiac safety and tolerability of these agents, including any relevant case reports, are reported systematically. Two nonselective 5-HT(4) agonists had reports of cardiovascular AEs: cisapride (QT prolongation) and tegaserod (ischaemia). Interactions with, respectively, the hERG cardiac potassium channel and 5-HT(1) receptor subtypes have been suggested to account for these effects. No cardiovascular safety concerns were reported for the newer, selective 5-HT(4) agonists prucalopride, velusetrag, naronapride, or for nonselective 5-HT(4) agonists with no hERG or 5-HT(1) affinity (renzapride, clebopride, mosapride). Conclusions:

5-HT(4) agonists for GI disorders differ in chemical structure and selectivity for 5-HT(4) receptors. Selectivity for 5-HT(4) over non-5-HT(4) receptors may influence the agent's safety and overall risk-benefit profile. Based on available evidence, highly selective 5-HT(4) agonists may offer improved safety to treat patients with impaired GI motility. (Tack et al, 2012)

Reviewer conclusions: *This publication provides reassurance on the safety of prucalopride and the absence of any correlation with QT interval prolongation.*

Frampton (2009) Prucalopride.

Prucalopride, a first-in-class dihydrobenzofuran-carboxamide derivative, is a potent, selective and specific serotonin 5-HT(4) receptor agonist with enterokinetic properties. Over a 12-week treatment period, prucalopride 2 and 4 mg once daily significantly improved bowel habit assessments (based on patient diary data) relative to placebo in three large, randomized, double-blind, multicentre trials in patients (aged 17-95 years) with severe chronic constipation, the majority of whom were women who experienced inadequate relief with previous therapies. There was no additional benefit with the 4 mg/day over the 2 mg/day dosage of prucalopride. Patient assessments of constipation symptoms and severity, treatment efficacy, satisfaction with bowel habit and treatment, and health-related quality of life were also significantly improved with prucalopride compared with placebo. The improvement in patient satisfaction with bowel habit and treatment was maintained for up to 24 months in open-label, multicentre, long-term follow-up studies. Prucalopride therapy was generally well tolerated; most adverse events in the 12-week studies were transient and of mild to moderate severity. In terms of cardiovascular tolerability, the incidence of QT interval prolongation with prucalopride at dosages of 2 and 4 mg/day was low and similar to that with placebo. Moreover, prucalopride at dosages up to 20 mg/day (10-fold higher than the recommended therapeutic dosage) had no clinically relevant effects on cardiovascular parameters in healthy volunteers. (Frampton, 2009)

Reviewer conclusions: *Among patients with normal baseline Fredericia-corrected QT (QTcF) intervals, post baseline QTcF values of 450–480 ms, 480–500 ms and >500 ms were observed in 2.5%, 0.5% and 0% of prucalopride 2 mg/day recipients (n = 604). 450-480. This result is not alarming as these variations are expected in small numbers within the normal ranges.*

Camilleri et al (2009) Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study.

Chronic constipation is common among nursing home residents. The aim of this study was to evaluate safety, tolerability and pharmacokinetics of the selective 5HT(4) receptor agonist prucalopride in elderly, chronically constipated patients in nursing homes. A multicentre, phase II, randomized, double-blind dose-escalation study in 89 elderly constipated nursing home residents treated with placebo, 0.5, 1 or 2 mg prucalopride once daily for 28 days was analysed. Adverse events, vital signs, ECG, Holter monitor and pharmacokinetics were assessed (Clinicaltrials.gov identifier: NCT00627692). Patients' mean age was 83 years; 88% had a history of cardiovascular diseases. Most frequent adverse events, at least possibly related to prucalopride, were diarrhoea and abdominal pain. Relative to placebo, there were

no differences in vital signs, ECG corrected QT interval, ECG morphology parameters, or incidence of supraventricular or ventricular arrhythmias on Holter monitoring. Plasma prucalopride concentrations increased proportionally with administered dose. Prucalopride up to 2 mg once daily for 4 weeks was safe and well-tolerated by constipated elderly patients, with no differences vs placebo in ECG or a range of Holter-monitoring parameters. (Camilleri et al, 2009)

Reviewer conclusions: *This publication provides reassurance on the safety of prucalopride and the absence of any correlation with QT interval prolongation.*

Post-marketing pharmacovigilance data review:

Case 1: This serious spontaneous report from Canada received on 17-JAN-2014 by a physician describes the occurrence of Atrioventricular block first degree, Drug interaction and Electrocardiogram QT prolonged in a 40 year-old female patient of unknown ethnicity taking Resotrans (Prucalopride succinate) for an unknown indication. Other suspect therapies included: METADOL (METHADONE HYDROCHLORIDE) for an unknown indication. The patient had no concurrent medical history. The past medical history for the patient included electrocardiogram normal. No allergy history for the patient was reported. No procedure history for the patient was reported. No information was provided for concomitant medications. The patient commenced treatment with Resotrans, 1 mg tablet, unknown frequency on an unknown date. The patient commenced treatment with METADOL, on an unknown date. On an unknown date the dose was 10 mg, three times a day. It was noted that the patient was taking Resotrans and METADOL for more than six months at the time of the events occurring. On an unspecified date, the patient experienced a cardiovascular problem, clarified as QT elevation and a first degree atrioventricular (AV) block. These events were noted to be a possible drug interaction between Resotrans and METADOL. Treatment, if any, and the outcome of the events were unknown. The action taken with the primary suspect therapy Resotrans was unknown. The action taken with the co-suspect therapy METADOL was also unknown. This report was considered serious for the following events: Atrioventricular block first degree and Electrocardiogram QT prolonged (Medically Significant). The event of drug interaction was considered non-serious. The causality assessed by a physician for the events of Atrioventricular block. first degree, Drug interaction, Electrocardiogram QT prolonged as Possible to Resotrans (Prucalopride succinate). Physician assessed the events (1st degree AV block, ECG QT prolongation) as not related to Resolor treatment, but related to the co-suspect drug Metadol (methadone). The label of methadone has cardia conduction effects listed as ADRs in Precautions section as follows: Cardiac Conduction Effects: Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. The Company's Pharmacovigilance Physician assessed the events (1st degree AV block, ECG QT prolongation) as not related to Resolor treatment, but related to the co-suspect drug Metadol (methadone). The label of methadone has cardia conduction effects listed as ADRs in Precautions section as follows: Cardiac Conduction Effects: Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. CA-EMA-20150325-sonalsoodp-150823545

Reviewer comment: *Methadone, know to prolong QT is more likely to have caused the event.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 2: 49 year old female was reported to have QT prolongation, nausea, vomiting, decreased appetite and a fall with citalopram, ondasetron and prucalopride. GB-MHRA-MIDB-2c4a4ace-83be-43b2-af92-d93cebe0c226

Reviewer comment: *case not assessable*

Case 3: 30 year old female was reported to have QT prolongation while on therapy with prucalopride and citalopram for irritable bowel syndrome. Concomitant medications included chlorpheniramine, etythromicin, ibuprofen and loperamide. Woman was also on Macrogol, mebeverine, naproxen, salbutamol, tramacet and trimethoprim. The adverse event of QTc prolongation occured after 68 days of citalopram therapy and after 8 months on prucalopride. The event involved hopsitalisation and the outcome was not reported. GB-MHRA-EYC 00111427

Reviewer comment: *Citalopram, known to prolong QT is more likely to have caused the event.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Active substance	BH criterium	Assessment
PRUCALOPRIDE	Strength of association	4.50 PRR, 3 ADR case reports 1 of which is not assessable and the other two with outcome uncertain
	Biological Plausibility	A modest. hERG inhibition in human embryonic kidney cells (HEK293) and Action Potential duration prolongation in perfused tissues were seen at very high doses highly unlikely to be achieved in man.
	Biological gradient	No increasing QT interval prolongation was seen with increasing doses of prucalopride.
	Experimental evidence and temporality	Temporal relationships in the two assessable cases were present but long drawn out. In the two cases prucalopride was given with drugs known to prolong the QT interval.
	Consistency	2 cases were counfounded and do not point to an association, preclinical, clinical and literature data all point against the association of QT prolongation with prucalopride.
	Specificity	Prucalopride has high affinity for and is highly specific to 5-HT4 receptors in the gut.
	Analogy	Prucalopride is the first of a new generation of selective, high-affinity 5-HT4 receptor agonists – no analogy can be drawn.
Overall assessment	***In the Eudravigilance database the association was disproportionally reported for this drug over others, and preclinical data demonstrates a mechanism of action although this occurred at plasma concentrations not achieved with therapeutic doses. Literature and case review do not support the relation.***	

Appendix 12:
Fingolimod

Fingolimod: Gilenya® 0.5 mg hard capsules

Date EU approval: 15th October 2009

Indication: Gilenya is indicated as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for the following adult patient groups:

- patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or:
- patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Availability in MT: available on the GFL

Currently authorised SmPC wording:

Section	Wording
4.3 Contraindications	*Not listed*
4.4 Warnings	*Not listed*
4.5 Interactions	*Not listed*
4.8 List of ADRs	*Not listed*
5.0 Pharmacology	*Not listed*

Number of reports in Eudravigilance database (PRR, CHI^2):

4.332148271	**13.68978324**	43.26033028	34.12581374

Gilenya is under additional monitoring in the EU. This means that it is being monitored even more intensively than other medicines.

Summary of company preclinical data

Cardiovascular effects

No in vitro effects were observed on platelet aggregation, cardiac action potential in sheep or rabbit purkinje fibres, QT interval prolongation or QRS in isolated pig hearts. An increased sinus frequency and a slight QT shortening (3%) were observed by both fingolimod and its active metabolite FTY720 P in isolated pig hearts. In isolated rabbit nodes, FTY720-P slightly but significantly decreased the spontaneously beating rate in sino-atrial (SA) node in two different studies by -8 and -12 % versus baseline and on atrioventricular (AV) node with a decrease in the spontaneously beating rate of -9 % versus baseline at 1000 nM. Conduction velocity, amplitude and duration were not significantly modified. Fingolimod inhibited hERG tail current from 200 ng/mL by 25.2 % in HEK293 cells and the active (S)-enantiomer of FTY720-P (AML629) inhibited hERG channel activity from 100 ng/mL by 18.1%, which is well above the human Cmax,ss at the therapeutic dose of 0.5 mg/day (3.4 ng/mL). In wistar rats, an increased diastolic and systolic blood pressure was observed at an oral dose of 1 and 10 mg/kg of FTY720 and decreased heart rate and sinus arrhythmia were observed at 10 mg/kg. In guinea pigs, an intravenous dose from 0.01 mg/kg caused sinus arrhythmia and 0.1 and 1 mg/kg decreased heart rate and blood pressure. The QT interval was prolonged as heart rate was decreased but there were no QTc prolongation observed.

Oral administration in conscious dogs caused a dose-dependent decrease in blood pressure at 0.3 and 1 mg/kg. No clear effect on heart rate was observed. In another oral dog study, doses from 5 mg/kg showed a decrease in heart rate (minimal effects in individual animals at 1 mg/kg) and an increase in blood pressure from 2.5 mg/kg. In monkeys dosed at 10 mg/kg orally, there was an increased systolic and diastolic blood pressure 4- 72 hours after administration with maximum increase after 6 hr (133.3 and 135.8% respectively) and a decreased heart rate 8-12 hr after administration by approximately 22%, compared to baseline, and an increased ECG T-wave potential in 2/4 animals that peaked 2, 6 and 8 hr post dose. Intravenous administration of the active (S)-enantiomer of FTY720-P (AML629) in rats showed a marked and transient sinus bradycardia with concomitant sinus arrhythmia and sinoatrial and/or atrioventricuar blocks and decreased heart rate at 0.1 mg/kg. There was a trend towards reversibility of these effects.

In guinea pigs administered intravenously with 0.01 mg/kg AML629, a decreased heart rate and blood pressure, prolonged PR and QT interval but no QTc prolongation was observed. At 0.1 mg/kg also sinus arrhythmia and ECG changes were noted.

Summary of company clinical data

In the thorough QT study in man a mild but significant prolongation of QTc interval was observed. These findings are considered an indirect effect related to the negative chronotropic effect induced by fingolimod in the initial phase of treatment. Outlier analysis of QTcB and QTcF in the pivotal, Phase III MS trials did not reveal a clear signal of QT prolongation with chronic dosing.

ECG findings

The most frequently observed findings in the 6 hours following administration of the first dose of fingolimod were ECG conduction and rhythm findings. AV conduction block was assessed primarily through Day 1 ECGs (at or around 6-hour timepoint) and, in a subset of patients, with continuous 24-hour Holter monitoring. A clear dose-dependent increase in the proportion of patients with first-degree AV block on the Day 1 ECG performed at 6 hours post-dose was seen. In the fingolimod 1.25 mg and 0.5 mg groups this was seen in 9.8% and 4.7% of the patients, respectively, compared to 1.5% for placebo and 2.8% for IFN β-1a (Group A). Second-degree Mobitz I AV block was seen in 0.7% and 0.2% of patients in the fingolimod 1.25 mg and 0.5 mg groups. In addition, 0.2% of the fingolimod

1.25 mg group had 2:1 AV block, whereas no patients in the fingolimod 0.5 mg, placebo or IFN β-1a groups reported 2:1 AV block.

This ECG data is similar to results using AE (adverse event) reports of second-degree AV block showing a dose-effect, a finding that is supported by data also in Group E in which the same proportions of patients with second-degree AV blocks, 0.6% on fingolimod 1.25 mg vs. 0.1% on fingolimod 0.5 mg, was seen as in Group A. On Day 2, one patient in the fingolimod 1.25 mg group, and no patients in the fingolimod 0.5 mg and placebo groups, had an AV Mobitz I block at 6 hours after the second dose. Second-degree Mobitz I AV block (Wenckebach) was detected in 17.9% (5/28) of fingolimod 5.0 mg patients, 7.1% (31/435) of 1.25 mg patients, 3.0% (12/398) in 0.5 mg patients, 1.8% (7/384) of placebo patients and no IFN β-1a patients (0/45). In addition, 2:1 AV block was reported in 3.4% (12/435) of patients on fingolimod 1.25 mg and 1.5% (6/398) of those on fingolimod 0.5 mg with no cases reported with placebo or IFN β-1a. Of the three patients with second degree AV block on Holter monitoring, all were receiving 1.25 mg. They were all symptomatic but recovered spontaneously within 24 hours. The increased incidence of conduction block with Holter monitoring compared to AE reporting or ECG results is expected given both the longer duration of observation and the direct ascertainment over the 24-hour interval. Of interest with respect to dose relationship in some of the company studies such as study 22, was the fact that on AE reporting, no cases of first- or second-degree AV block were reported in the highest 5 mg dose group (n=94). However, in the 28 patients in whom Holter monitoring was conducted in this dose group, 17.9% had second-degree AV block Mobitz I (Wenckebach) detected, supporting the dose-response relationship of this adverse drug reaction.

One transient third-degree, narrow complex, AV block was reported in a 40-year-old female patient participating in the extension phase of Study D2302. Two hours after the first dose of fingolimod 1.25 mg, her pulse was irregular and ECG showed second degree Type I AV block with a heart rate of 55 bpm. At 3 hours post-dose, she was noted to have pallor and apparent loss of consciousness for approximately 30 seconds. At the time of the event, cardiac monitoring showed third-degree AV block which lasted for 30 seconds. The patient recovered spontaneously and then was treated with a single dose of atropine (0.125 mg, IV). She made a complete recovery with normal sinus rhythm (61 bpm) within 24 hours of onset of this event.

Scientific literature

Turri et al (2017) QTc interval in patients with multiple sclerosis: an inference from the insula of Reil?

Background: The aim of this study was to investigate the correlation between the duration of the QTc interval and the brain lesion load at the level of the structures involved in superior autonomic control (insula, cingulate cortex and amygdala-hippocampus) in multiple sclerosis (MS) patients. Methods: Thirty-one consecutive patients with relapsing-remitting MS were recruited. The QT interval was measured manually in all 12 leads by a single blinded observer, with the longest QT value adjusted for heart rate by using the Bazett's formula. All patients performed a brain magnetic resonance imaging (MRI) scan including three-dimensional double inversion recovery and three volumetric fast-field echo sequences. The following MRI measures were obtained: (i) global and regional cortical thickness (CTh); (ii) white matter lesion load volume; (iii) cortical damage blindly assessed by a trained observer who assigned, on the basis of the number of cortical lesions, a score from 0 to 5 for each of the brain areas analysed. Results: In all, 16% of the patients had an increased QTc interval. The QTc interval was correlated with disease duration, cortical insular lesion volume and grey matter lesion volume in the three examined areas and inversely correlated with global and insular CTh. Conclusions: An increased QTc interval in patients with MS may have a cerebral origin possibly driven by involvement of the insular cortex. With the recent introduction in clinical practice of treatments with potential cardiac effects such as fingolimod, the recognition of a long QTc interval could be clinically crucial and should encourage appropriate electrocardiographic monitoring in order to prevent the risk of malignant ventricular pro-arrhythmia and iatrogenic sudden death.

Linker et al (2016) Cardiac Safety Profile of First Dose of Fingolimod for Relapsing-Remitting Multiple Sclerosis in Real-World Settings: Data from a German Prospective Multi-Center Observational Study.

Background: Fingolimod was the first oral therapy approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Due to its action on cardiac sphingosine 1-phosphate receptors, fingolimod is leading to a transient decrease in heart rate (HR) and the occurrence of rare and asymptomatic self-limited atrioventricular (AV) blocks. This German non-interventional clinical study aimed to assess the cardiac safety profile in RRMS patients during at least 6 h after the initial treatment or restart after interruption of fingolimod in real-world settings. Method: The GoCARD study was a prospective, multi-center non-interventional study which was conducted in neurological and other medical practices or hospitals, qualified to routinely assess electrocardiogram (ECG) findings. Data were collected through interviews, clinical evaluations (notably ECGs), and laboratory tests. Medical history, vital signs, and a 12-lead ECG were assessed before fingolimod administration. After the first dose, a 6 h ECG was performed and vital signs (blood pressure and HR) were measured hourly. The occurrence of bradycardia (HR ≤45 beats per minute [BPM]), AV blocks (2nd degree Mobitz type I or higher), and corrected QT interval (QTc) intervals was also documented. Results: More than 95% of physicians adhered to the cardiac monitoring recommendations. The observation of 217 patients in 42 study centers showed that while 35.9% of the patients had any cardiac risk profile, none of them experienced a bradycardia during the 6 h post-dose observation. Overall, only 1.8% of all patients displayed bradycardia (HR ≤45 BPM) during 6 h after treatment initiation. Moreover, in this cohort, none of the patients showed a new or persistent onset AV block (2nd degree Mobitz type I or higher) or QTc ≥500 ms. Conclusion: Altogether, these data confirm that the first-dose observation after fingolimod initiation is usually uneventful (even in patients with pre-existing cardiovascular risk factors of this cohort) and that the rarely observed events remained asymptomatic and self-limited. (Linker and Wendt, 2016)

Tocci et al (2016) Tp-Te interval predicts heart rate reduction after fingolimod administration in patients with multiple sclerosis.

Background: FTY720 (Fingolimod) is an immunosuppressive drug, which provides favourable effects in patients with multiple sclerosis (MS), albeit it induces heart rate (HR) and blood pressure (BP) reductions. Therefore, we tested potential factors able to predict HR response in MS patients treated with fingolimod. Method: We analysed patients with MS followed at our Neurology Outpatient Clinic from May 2013 to June 2015. All patients underwent BP measurements and 12-lead ECG before and 6-h after drug administration. At these time intervals, conventional and new ECG indexes for cardiac damage, including Tp-Te interval, were measured. Univariate and multivariate analyses were performed to test the outcome of HR reduction more than median difference between baseline and final observations. Results: 69 outpatients with MS (46 males, age 35.1±9.4years, BP 119.0±12.7/73.0±9.3mmHg, HR 73.5±11.4bpm) were included. No relevant adverse reactions were reported. Fingolimod induced progressive systolic (P=0.024) and diastolic (P<0.001) BP, as well as HR (P<0.001) reductions compared to baseline. Prolonged PQ (150.4±19.5 vs. 157.0±19.5ms; P<0.001), QT (374.9±27.0 vs. 400.0±25.8ms; P<0.001), Tp-Te (1.8±0.3 vs. 1.9±0.3mm; P=0.021), and reduced QTc (414.4±24.4 vs. 404.5±24.5ms; P<0.001) intervals were also recorded at final observation. Baseline HR, QT and Tp-Te intervals provided prognostic information at univariate analysis, although Tp-Te interval resulted the best independent predictor for HR reduction at multivariate analysis [0.057 (0.005-0.660); P=0.022]. Conclusions:This study firstly demonstrates that prolonged Tp-Te interval may identify those MS patients treated with fingolimod at higher risk of having significant, asymptomatic HR reduction during clinical observation. (Tocci et al, 2016)

Bermel et al (2015) Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors.

Selective serotonin-reuptake inhibitors (SSRIs), commonly administered for depression and anxiety in patients with multiple sclerosis, are associated with QT interval prolongation. Fingolimod (FTY720; Gilenya(®), Novartis Pharma AG) is a first-in-class sphingosine 1-phosphate receptor modulator approved for relapsing forms of multiple sclerosis. Fingolimod first-dose administration is associated with a transient, generally asymptomatic, slowing of heart rate, which may also prolong QT interval. This posthoc analysis compared cardiac outcomes in over 3300 patients with relapsing multiple sclerosis who were or were not receiving SSRIs during fingolimod treatment initiation, including a subset of patients receiving citalopram or escitalopram. Vital signs were recorded hourly for 6h, and electrocardiograms were obtained pre-dose and 6 h post-dose. Changes in mean hourly heart rate from baseline (pre-dose) to 6 h post-dose were similar among patients not receiving SSRIs (fingolimod 0.5 mg, -7.5 bpm; placebo, 0.0 bpm) and those receiving SSRIs (fingolimod 0.5 mg, -6.6 bpm; placebo, 0.3 bpm). In patients treated with fingolimod 0.5 mg, the mean change in corrected QT interval from baseline to 6 h after treatment initiation was under 10 ms, and few patients had absolute corrected QT intervals of over 450 ms (men) or 470 ms (women), calculated according to Bazett′s or Fridericia′s correction methods, irrespective of whether or not they were receiving an SSRI; similar findings were reported in the placebo group. Co-administration of SSRIs and fingolimod was not associated with an increased incidence of any electrocardiogram findings compared with fingolimod therapy alone, and the majority of patients receiving fingolimod (83-86%) were discharged from first-dose monitoring at 6 h irrespective of whether they were also receiving SSRIs. These analyses provide reassurance that concomitant use of SSRIs does not affect cardiac outcomes associated with fingolimod treatment initiation. (Bermel et al, 2015)

Yagi et al (2014) Analysis of Onset Mechanisms of a Sphingosine 1-Phosphate Receptor Modulator Fingolimod-Induced Atrioventricular Conduction Block and QT-Interval Prolongation.

Fingolimod, a sphingosine 1-phosphate (S1P) receptor subtype 1, 3, 4 and 5 modulator, has been used for the treatment of patients with relapsing forms of multiple sclerosis, but atrioventricular conduction block and/or QT-interval prolongation have been reported in some patients after the first dose. In this study, we directly compared the electropharmacological profiles of fingolimod with those of siponimod, a modulator of sphingosine 1-phosphate receptor subtype 1 and 5, using in vivo guinea-pig model and in vitro human ether-a-go-go-related gene (hERG) assay to better understand the onset mechanisms of the clinically observed adverse events. Fingolimod (0.01 and 0.1mg/kg) or siponimod (0.001 and 0.01mg/kg) was intravenously infused over 10min to the halothane-anaesthetized guinea pigs (n=4), whereas the effects of fingolimod (1μmol/L) and siponimod (1μmol/L) on hERG current were examined (n=3). The high doses of fingolimod and siponimod induced atrioventricular conduction block, whereas the low dose of siponimod prolonged PR interval, which was not observed by that of fingolimod. The high dose of fingolimod prolonged QT interval, which was not observed by either dose of siponimod. Meanwhile, fingolimod significantly inhibited hERG current, which was not observed by siponimod. These results suggest that S1P receptor subtype 1 in the heart could be one of the candidates for fingolimod- and siponimod-induced atrioventricular conduction block since S1P receptor subtype 5 is localized at the brain, and that direct IKr inhibition may play a key role in fingolimod-induced QT-interval prolongation. (Yagi et al, 2014)

Rossi et al (2015) The autonomic balance predicts cardiac responses after the first dose of fingolimod.

Background: Predictive markers of cardiac side effects would be helpful for the stratification and individualized monitoring of multiple sclerosis (MS) patients prescribed with fingolimod. Objective: To test whether the autonomic balance predicts a cardiac response after the first dose of fingolimod. Method: A total of 55 consecutive relapsing-remitting MS (RRMS) patients underwent 'head-up tilt', Valsalva maneuver, deep breathing and handgrip tests before their first dose of fingolimod. The normalized unit of the high frequency (HF) component (HF normalized units; HFnu), reflecting mostly vagal activity; and the low frequency (LF) component (LF normalized units; LFnu) reflecting mostly sympathetic activity, were considered for the analysis of heart rate (HR) variability. The patients' HR and electrocardiographic parameters ((the interval between P wave and ventricular depolarization (PR); the interval between Q and T waves (QT)) were recorded during 6-hour post-dose monitoring. Results: We found significant correlations between measures of parasympathetic function and fingolimod-induced bradycardia. Subjects with higher Valsalva ratio and HR variation during deep breathing had, in fact, nadir HR ≤ 50 beats/minute (bpm) after the first fingolimod dose. Conversely, significant negative correlations were found between measures of sympathetic function and fingolimod-induced PR interval increase. Subjects with lower LFnu at rest and less increase of blood pressure on the handgrip test showed a PR interval increase > 20 ms after fingolimod. Conclusion: Assessing autonomic control of cardiovascular functions can be useful to predict cardiac effects after the first fingolimod dose. (Rossi et al, 2015)

Schmouder et al (2006) FTY720: placebo-controlled study of the effect on cardiac rate and rhythm in healthy subjects.

The purpose of this double-blind, placebo-controlled study was to measure the effects of FTY720, a novel immunomodulator, on heart rate and rhythm in healthy volunteers. Subjects (n = 66) were randomized to FTY720 1.25 mg or 5 mg or placebo administered once daily for 7 days. Continuous telemetry revealed an acute, dose-dependent decrease in mean heart rate (10-bpm decrease vs placebo)

following the first dose of FTY720, with a nadir generally 4 hours postdose. Although a persistent FTY720-related decrease in heart rate was measured from day 2 to day 7, additional doses of FTY720 after day 2 resulted in no further incremental decreases. Mean PR interval increased by approximately 8 to 10 msec in FTY720-treated subjects on day 1. FTY720 did not increase the QRS or QT interval. These results confirm that the first dose of FTY720 has a mild to moderate negative chronotropic effect. (Schmouder et al, 2006)

Post-marketing pharmacovigilance data review:

Case 1: concerns a 35-year-old female patient. The patient's medical history and concomitant medication were not reported. This patient received Gilenya (fingolimod) 0.5 mg daily since 20 Nov 2011 for multiple sclerosis. On the day of FDO (first dose observation) on 20 Nov 2012, after 6 hours into FDO, the patient's heart rate decreased to 54 bpm, blood pressure decreased to 112/70 and QT interval was shortened from 408-407. Patient developed bradycardia due to which she was hospitalized for further monitoring. Causality was reported as suspected to the treatment of Gilenya. US-002147023-PHEH2012US022937

Reviewer comment: *QT interval shortening of 1 ms is not considered to be a significant adverse event.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 2: concerns a 25-year-old female patient. The patient did not had any relevant medical history or received any past drug. Concomitant medication included Trazodone. This patient received Gilenya (fingolimod) on 06 Dec 2012 at 08.40 for multiple sclerosis at a daily oral dose of 0.5 mg. Her heart rate at the baseline was 88 bpm. She complained of palpitations on 06 Dec 2012 at 10:10 pm with no chest pain. Minimum heart rate measured at the event was 68 bpm. The physical examination was unremarkable. The electrocardiogram (EKG) showed sinus rhythm with premature atrial contractions (PAC). Her heart rate was at 78 and QTC was at 307. She did not receive any treatment for the event. The treatment with Gilenya was ongoing. The symptoms resolved by discharge on 06 Dec 2012. The EKG was without PAC or other blocks. US-002147023-PHEH2012US024203

Reviewer comment: *temporality is suggestive, however rechallenge was negative as treatment was ongoing and QT interval shortening resolved spontaneously.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R-	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: refers to a 50 year old male patient. The Patient had history of multiple sclerosis, myxomatous mitral valve and slightly elevated blood pressure who presented because of abnormal EKG that was found prior to initiation of Gilenya. The patient denied any symptoms of chest pain, shortness of breath or palpitations. He stated that he was a competitive runner (aerobic athlete) in his younger years, but continued to arise for exercise 5 days per week. He did not get any exertion symptoms. He did not react well to the injectable multiple sclerosis medications, so he was hoping that oral medication Gilenya might help him. He was a former smoker and used tobacco 4 years. He was taking moderate 4 cup coffee daily. Patient had no known drug allergy. The patient stated that he had mitral valve prolapse as an adolescent, while he did not have prolapse of valve, he did not have a myxomatous looking valve. This was likely of no consequence as the valve opens well and had only trivial regurgitation. Borderline LVH was likely secondary to his athletic nature. On 03 Jun 2014, prior to Gilenya patient had an ectopic atrial rhythm with a rate of 57 bpm. There was evidence of right axis

deviation and poor R wave progression that might be secondary to the abnormal focus of the rhythm. On 14 Jul 2014, prior to Gilenya administration, his EKG showed heart rate at 57 BPM, PR interval at 160 ms, QRS interval at 83 ms, QT interval at 438 ms and QTc interval at 426 ms with sinus bradycardia with coupled PACs (premature atrial contractions). The cardiologist (external expert) assessed the ECG as low atrial at 57 bpm. This patient was taking Gilenya (fingolimod) from 14 Jul 2014 for treatment of relapsing remitting multiple sclerosis at a dose of 0.5 mg daily. On 14 Jul 2014, after starting Gilenya patient had abnormal EKG (asymptomatic) at the end of 6 hours at FDO. Post dose EKG showed heart rate at 44 BPM, PR interval at 208 ms, QRS interval at 90 ms, QT interval at 360 ms and QTc interval at 308 ms. On 14 Jul 2014, diagnostic test revealed he had bradycardia as low as 39 bpm, with clear 2:1 or complete heart block on the accompanying strips. On 14 Jul 2014, EKG revealed that he had sinus bradycardia at a rate of 44 bpm and 49 bpm, high voltage in the cardial leads. Compared with the previous EKG, the patient was now in a normal sinus rhythm compared to ectopic atrial rhythm. On 14 Jul 2014, the patient had a Wenckebach 2 but was asymptomatic. Upon follow up on 30 Jul 2014, cardiologist stated that the patient had potential complete heart block after initial dose of Gilenya. The patient went yesterday for his first dose with the normal 6 hours monitoring. He felt well during the entire time without any symptoms of lightheadedness, passing out or fatigue. However, the person reading the monitor remotely suggested that the patient had 2 1 AV block and some AV dissociation consistent with 3rd degree AV block. Because of this the patient was not given another dose of Gilenya and was sent to cardiologist's office for evaluation. The patient continued to felt well. He stated that after leaving the office, he ran to get his son and had slow down a little bit, but that was normal on a hot day. He ran for an hour and half of exercise as well without any problems. Upon follow up on 11 Sep 2014, cardiologist (external expert) assessed 12 lead ECG shows low atrial rhythm at 44 bpm with first degree AV block. Rhythm strip uninterpretable due to artifact. Action taken with Gilenya was discontinued. Outcome of the event Wenckebach 2 was reported as completely recovered on 16 Jul 2014. US-002147023-PHEH2014US014596

Reviewer comment: *temporality is positive however there were EKG abnormalities prior to first administration of Gilenya possibly due to the mitral valve prolapse and regurgitation.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 4: refers to a 57-year-old male patient. The patient received Gilenya (fingolimod) capsule for the treatment of multiple sclerosis from 30 Dec 2015 at a dose of 0.5 mg, QD (oral). The patient's baseline EKG-QTc interval was 466 and post FDO the level was 453 on 30 Dec 2015 (electrocardiogram QT interval shortened). The outcome of the event was reported as condition unchanged with no side effects. The patient was stable. US-002147023-PHEH2015US027561

Reviewer comment: *Outcome using French tool is Uncertain. There is sparse information to assess*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

FINGOLIMOD	
BH criterium	**Assessment**
Strength of association	13.69 PRR 4 ADR Case reports, all uncertain outcome Pubmed literature search yielded 6 articles relevant to QT effects.
Biological Plausibility	Fingolimod and its s enantiomer blocked the hERG channel and Ikr current in *in vitro* laboratory models (HEK293 cells) by 25.2% and 18.1% respectively. An increased sinus frequency and a slight QT shortening (3%) were observed by both fingolimod and its active metabolite FTY720 P in isolated pig hearts. This therefore provides a plausible mechanism for QTc interval prolongation and arrhythmia but not for QT interval shortening.
Biological gradient	Increased blockade of hERG was not seen at increased dose.
Experimental evidence and temporality	Temporal relationships between the events and the initiation of treatment was present in all 4 postmarketing cases, however the QT shortening was insignificant in 1 case, and in the other 3 cases previous cardiac valve disease, minimal information and negative rechallenge did not provide any support for the association. In the literature Schmouder et al (2006) studied fingolimod effects on cardiac rate and rhythm in healthy subjects but did not specifically investigate the QT interval. The results showed that the first dose of has a mild to moderate negative chronotropic effect. (Schmouder et al, 2006) as is listed in the SPC. Nonetheless, Yagi et al (2014) investigated QT prolongation effects of fingolimod in a study analyzing the Onset Mechanisms of a Sphingosine 1-Phosphate Receptor Modulator Fingolimod-Induced Atrioventricular Conduction Block and QT-Interval Prolongation. They found that at high doses, fingolimod prolonged QT interval, and significantly inhibited hERG current. No evidence was mentioned on QT shortening (Yagi et al, 2014) In a study by Bermel et al (2015), fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors comparing cardiac outcomes in over 3300 patients with relapsing multiple sclerosis did not find any QT shortening effects.(Bermel et al, 2015) Rossi et al (2015) investigated both QT and PR intervals in an predictive cardiac response study after the first dose of fingolimod and found that while PR intervals increase > 20 ms after fingolimod, no effects were observed on the QT interval. (Rossi et al, 2015) Linker et al (2016) observed 217 patients in 42 study centers and concluded that the first-dose observation after fingolimod initiation is usually uneventful even in patients with pre-existing cardiovascular risk factors of this cohort and unlikely to cause QT shortening. They report that rarely observed events remained asymptomatic and self-limited. (Linker and Wendt, 2016)

	Tocci et al (2016) investigated a model using Tp-Te intervals to predict heart rate reduction after fingolimod administration in patients with multiple sclerosis and found that rather short QTc (414.4±24.4 vs. 404.5±24.5ms; P<0.001) intervals were recorded but which do not fall under the criteria of short QT (400ms or less) (Tocci et al, 2016) Finally, Turri et al (2017) investigated QTc intervals in patients with multiple sclerosis and there correlation with brain lesions. They found that an increased QTc interval in patients with MS may have a cerebral origin possibly driven by involvement of the insular cortex.
Consistency	All post marketing cases originated from the US.
Specificity	Fingolimod and its metabolite were found to bind the human ether-a-go-go-related gene (HERG) potassium channel, which provides a plausible mechanism for QTc interval prolongation and arrhythmia but not for QT interval shortening.
Analogy	Other antipsychotic QTc interval-prolonging/arrhythmic drugs that also bind to HERG provided an analogy for loxapine causing QTc interval prolongation/arrhythmia via this mechanism.

Overall assessment:

Fingolimod is known to prolong the QT interval but has been reported in a few cases to shorten it as well. This was seen by the statistical disproportionate reporting of QT interval shortening with this drug. Upon investigation the cases reported were uncertain and confounded and did not have sufficiently robust information. There is nothing in the literature to support the association and pre clinical data does not reveal a hERG attenuating effect. Therefore there is no evidence to support the association between Fingolimod and QT shortening.

Appendix 13:
Olanzapine

Olanzapine: ZYPREXA 2.5 mg film-coated tablets

Mechanism of action: Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharinmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α1 adrenergic; and histamine H1 receptors.

Date EU approval: 16th November 1997

Indication: Olanzapine is indicated for the treatment of schizophrenia, moderate to severe manic episodes and prevention of recurrence in patients with bipolar disorder.

Availability in MT: available on the GFL

Currently authorised SmPC wording relative to short QT:

Section	Wording
4.3 Contraindications	Not listed
4.4 Warnings	Not listed
4.5 Interactions	Not listed
4.8 List of ADRs	Not listed
5.0 Pharmacology	Not listed

Statistics (PRR, CHI^2):

3.688354725	**9.086285287**	22.38412151	34.00536645

Summary of company preclinical and clinical data

The effects on hERG were not studied in the preclinical dossier part for olanzapine since it was authorised in 1997, ie prior to the mandating of hERG studies by ICH S7B and E14.

Scientific literature

Suzuki et al (2014) Changes in PR and QTc intervals after switching from olanzapine to risperidone in patients with stable schizophrenia

In this study the differences between the effects of olanzapine (OLZ) and risperidone (RIS) on PR and QT intervals among patients with stable schizophrenia were analyzed using a cohort analysis. Methods Twenty-one subjects treated with OLZ were enrolled in the study. Following baseline assessments, which included PR and QT intervals, OLZ was switched to RIS for each subject. The same parameters were evaluated following the switch to RIS. Results All patients who had been treated with OLZ were successfully switched to RIS. In all patients, we observed a significant decrease in PR interval ($t = 2.397$, $P = 0.029$) and no change in either QTc or RR interval. In female patients, the QTc interval was significantly decreased ($t = 3.495$, $P = 0.008$) following the switch, while in male patients, the QTc interval did not change. No patients showed a PR interval of >200 ms or a QTc interval of >500 ms. Conclusion OLZ treatment has a greater prolonging effect on PR and QT intervals compared with RIS. Careful attention may need to be paid to the cardiac conduction system in addition to QT prolongation during OLZ treatment.

Variable	Olanzapine treatment	Risperidone treatment	*P*-value
Female	410.3 ± 9.5	392.1 ± 14.4	0.008

Reviewer conclusions: *This study shows a significant reduction in the QT interval of the recruited female patients. This effect was not observed in the risperidone arm.*

Shafti et al (2014) A Comparative Study between Olanzapine and Risperidone Regarding Drug-Induced Electrocardiographic Changes.

Among atypical antipsychotics, none has been linked to torsade de pointes. In the present study, the electrocardiographic changes induced by olanzapine have been compared with risperidone. Method and Materials. 268 patients were entered into an open study for random assignment to olanzapine or risperidone. ECG was taken at baseline and at the end of the treatment. The parameters that had been assessed included Q-T interval (corrected = Q-Tc) and other related parameters. Correction of the observed Q-T interval was done according to Frederica's formula (QTcF). Results: While 14.86% and 25% of the cases in the olanzapine group showed prolongation and shortening of QTcF, respectively, comparable changes in the risperidone group were restricted to its prolongation (32.5%). Comparison of means between baseline QTcF of risperidone group versus its posttreatment measurement showed a significant increment . Also, the quantity of cases with shortening of QTcF in the olanzapine group was significantly more than its opposite. Conclusion: Comparable propensity of olanzapine and risperidone for induction of electrocardiographic changes demands adequate cautiousness by clinicians, particularly with respect to shortening of Q-T interval, which was mainly noticeable in the olanzapine group.

Reviewer conclusions: *This study shows a significant reduction in the QT interval of the recruited female patients. This effect was not observed in the risperidone arm.*

Post-marketing pharmacovigilance data review:

Case 1: 32-year old asian female patient who developed atrioventricular block, qt shortened, and experienced a feeling of residual urine following the use of olanzapine (zyprexa) for schizophrenia. As concomitant drugs, she was taking chlorpromazine/promethazine hydrochloride/phenobarbital, flunitrazepam, polycarbophil calcium, risperidone, zotepine, biperiden, sennoside, quetiapine fumarate, chlorpromazine, and distigmine bromide. The patient had no history of adverse drug reactions, and the patient did not smoke. She was concurrently suffering from mild duodenal ulcer since approximately 1996. In approximately the autumn of 1996, the patient developed severe schizophrenia including hallucinations, delusions, and decreased activity. Approximately in 1996, she started haloperidol 18mg/day and biperiden 6mg/day. On 14-apr-2000, she visited the reporter's hospital. On 19-may-2000, haloperidol was discontinued, and she started chlorpromazine 150-300mg/day. On 09-jun-2000, she started risperidone 4-12mg/day. The first electrocardiogram on 11-aug-2000 revealed ischaemic heart disease (±) from the anterior to lateral. In october 2000, she started zotepine 100-300mg/day. An electrocardiogram on 13-feb-2001 confirmed lateral ischaemic heart disease. The patient also had a history of low potassium. On 31-may-2001, risperidone was discontinued. On 07-jun-2001, chlorpromazine was discontinued. On 08-jun-2001, she started olanzapine 10-12.5mg/day. On 22-jun-2001, she started distigmine bromide 2 tablets/day. She was found to have a shortened qt and lateral ischaemic heart disease (±) on 11-jul-2001 and 12-sep-2001. On 20-sep-2001, zotepine was discontinued. On 09-nov-2001, ischaemic heart disease (±) was once again confirmed. On 26-dec-2001, she developed the first-degree atrioventricular block, and ischaemic heart disease (±) was again confirmed. She did not have any subjective symptoms in the chest, but she did experience a feeling of residual urine. On 09-jan-2002, she developed atrioventricular block (the second degree), and anterior ischaemic heart disease was confirmed. On 11-jan-2002, she started quetiapine fumarate 200-400mg/day. On 07-feb-2002, olanzapine was discontinued. On 13-feb-2002 and 12-mar-2002, second-degree atrioventricular block was confirmed. Distigmine and quetiapine had been maintained. She had been hospitalized for the sixth time since she first visited the reporter's hospital on 14-apr-2000. On 08-apr-2002, the atrioventricular block continued. JP-ELI_lilly_and_company-US_020281780

Reviewer comment: *Confounded case. A positive temporality, unknown dechallenge and underlying ischaemic heart disease allows for an uncertain causality assessment.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

Case 2: A 43-year-old female patient, a teacher, who has been raising alone her daughter who is a teenager. The onset of the disease had a neurotic character with undefined functional pains, such as headache, insomnia. And after that, severe psychotonic symptoms occurred. She was hospitalized in a psychiatry hospital without her approval. Ever since, she has been hospitalized in the psychiatry hospital, that is for approximately one year. Delusions of nihilism and cenesthetic hallucinations - false perceptions referring to the absence of the heart and of the internal organs, and delusions about punishment, guilt and courtesy - prevailed. She was refusing food, drink, she had a negative attitude, she was agitated. Periodically, some catatonia states occurred, such as oneiroid stimulation, especially

at night, or she had states of catatonic stupor. It was necessary to use protective means such as restraining belts due to her self-aggressive behaviour. She was treated with classical neuroleptics (haloperidol up to 15 mg/day, perzine up to 600 mg/day, levomepromazine up to 150 mg/day), and after that urinary retention occurred. After that she was treated with atypical neuroleptics, such as amisulpirid up to 600 mg/day, sulpiride up to 400 mg/day, risperidone up to 9 mg/day. Extrapyramidal symptoms and hyperprolactinemia occurred. Injections with aripiprazole (up to the dose of 30 mg/day) were applied, after which a stimulation occurred. The administration of olanzapine (up to 15 mg/day) and quetiapine (up to 800 mg/day) had no effect. Significant decreases of the blood pressure occurred after quetiapine. After the administration of ziprasidone in a dose of up to 160 mg/day, a significant state of stimulation occurred. Within the third-line procedure, after the application of the protocol for high need intervention (the patient did not agree with it) 11 electrical sessions were carried out which only led to the cessation of the symptoms of catatonic stupor, but delusions continued to occur. Valproic acid was added and after that it was noted a decrease of leukocytes up to 2900, and therefore its administration was discontinued. Sertindole was added gradually up to 20 mg/day, and after that it was obtained an improvement of the general condition and a cessation of the symptoms. Before adding sertindole to the therapy, based on the EKG which was performed, the length of QTc interval was 216 ms. The oneiroid type nocturnal disorders of consciousness continued to occur. After 3 days, clozapine was added gradually in a dose of 600 mg daily at night, and this led to the normalization of the sleep during the night. The patient was able to participate to the occupational therapy, to walk, she started taking care of her own hygiene. Leukopenia withdrew, appetite returned, prolactin level returned to normal and menstrual cycle started to occur, she did not have any problems with urine retention, her general condition improved. Due to the low blood pressure of 90/60, 2,5 mg of midodrine was added, and after that it was noted an improvement of the value of the blood pressure. During the treatment, sertindole was combined with clozapine, EKG was regularly performed, QTc interval reached a mean value of 225 ms." The outcome of hyperprolactinemia, extrapyramidal symptoms and blood pressure decreased was reported as improved at the time of this report. The outcome of urinary retention and leukocyte count decreased was reported as recovered at the time of this report. This case was considered as serious because the ADRs were medically significant.The case is rated as serious, unexpected and unassessable due to insufficient information regarding temporal association between suspect drug administration and onset of the events. Sender's comment: Based on the known safety profiles of risperidone, quetiapine, olanzapine and ziprasidone and the temporal relationship a possible contribution to the development of these events cannot be excluded. Based on the temporal relationship a possible contribution from valproate cannot be excluded. The events are extrapyramidal symptoms, hyperprolactinemia, agitation, leucopenia and QT shortening. It is to be noted in passing that most or all of these drugs have a safety profile that includes QT-prolongation but not QT-shortening. PL-EMA-20131031-chiragevhp-091428081

Reviewer comment: *temporality is consistent with a number of drugs but could be related to olanzapine use. Dechallenge from olanzapine did not resolve the situation. Outcome using FCA is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S2
Result	I1	Uncertain	

Case 3: concerns an adult female patient (mean age 25.63 years +/- 6.01) of unknown origin. Medical history included: Schizophrenia. Concomitant medications were not reported; no other concomitant psychotropic drug was permitted during the assessment. The patient received olanzapine 5 mg per day at baseline up to 10 mg/day at the end of the first week with weekly interval increments of 5mg and according to the clinical situation up to 25mg at week five for treatment of schizophrenia beginning on an unspecified date. On an unknown date, at the end of treatment and just before discharge (in the sunrise before initiation of daily prescription), a standard 12 lead surface ECG was taken. The results

showed a left anterior hemiblock in accompany with mild shortening of QTcF (0.01 sec). The events were considered serious by the company for medical significance. Information regarding corrective treatment, outcome of the events and status of the olanzapine was not provided. In the opinion of the reporting authors, the events were related to the olanzapine treatment. IR-eli_lilly_and_company-ir201411005629

Reviewer comment: *The shortening of the QT interval reported in this case was of 10ms but it is not stated what the original QT interval was. It is therefore difficult to categorize as QT shortening.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Case 4: concerns a 35-year-old male patient with a medical history of schizophrenia. The patient received olanzapine long acting intramuscular (LAIM) (Zypadhera) 405 mg, every 28 days, intramuscularly, indicated for schizophrenia, beginning on 13Feb2015. On 11Feb2016, one year after beginning of olanzapine LAIM treatment, one hour and a half after the 13th injection, patient experienced sedation and agitation episodes after olanzapine LAIM injection and during the monitoring, reported as post injection syndrome (probable therapeutic accident with the product leaking into the intravenous network) (as reported). It was reported that the patient had to be physically restrained. The patient also presented confusion with difficulty speaking, tachycardia and heart rate of 140bpm at 16h00. The patient was hospitalized due to the events for cardiac monitoring. Upon admission, patients blood pressure was 131/84 (units and normal ranges were not provided), heartbeat of 130bpm at 17h00 (normal ranges were not provided) and miosis. The patient underwent an electrocardiogram, presenting QTc of 400ms (normal values 450ms) at 19h00 and 366ms at 22h00. Also underwent a biological investigation which presented normal results. Negative troponin and normal creatinine phosphokinase (CPK). There was no sign of neurological focalization. In the same day at 22h00 heartbeats decreased down to 110ppm. On 12Feb2016 the patient went back to the psychotherapy center. Patient had a frank improvement of symptoms, his vitals were normal, and heart rate was at 103 bpm. It was reported that the patient did not remember what had happened the night before at all (as reported). He was scared and experienced a sensation of passing out (as reported). There was persistence of confusional and extrapyramidal elements (mainly dysarthria). Patient recovered from the events of sedation and agitation within 24 hours.
On 15Feb2016 patient was discharged as the patient was asymptomatic.On unknown date the olanzapine LAIM was switched to paliperidone palmitate. All outcomes for events were reported as recovered. FR-ELI_LILLY_AND_COMPANY-FR201602005425

Reviewer comment: *Temporality is very delayed (time from drug to event aproximatly one year) Outcome using French tool is Uncertain.*

Causality Assessment (French Method)			
Chronological criteria		Semiological criteria	
Challenge	Compatible	Symptoms	Very suggestive
Rechallenge	R0	Lab Test	L0
Dechallenge	C2	Alternate	S1
Result	I1	Uncertain	

Olanzapine

BH criterium	Assessment
Strength of association	9.03 PRR 4 post-marketing ADR Case reports all with outcome uncertain 2 articles reporting QT shortening.
Biological Plausibility	There was no preclinical data available in the dossier to assess the effects on hERG since the approval of this product occurred prior to the mandatory requirement to test new active substances for their effects on QT.
Biological gradient	Increased QT interval shortening was not seen with increasing doses of olanzapine from the limited post-marketing studies or cases.
Experimental evidence and temporality	Of the 4 cases assessed, all had a temporal relationship between the events and the initiation of treatment however cases were often confounded by lack of information, lack of dechallenge, or a very small decrease in the QT interval. However, two studies were found to connect olanzapine with short QT. In the Suzuki study (2014) changes in PR and QTc intervals after switching from olanzapine to risperidone in patients with stable schizophrenia were investigated. It was found that all in female patients, the QTc interval was significantly decreased ($t = 3.495$, $P = 0.008$) following the switch, while in male patients, the QTc interval did not change. The initial QT interval in female patients decreased from 410.3 ± 9.5 to 392.1 ± 14.4 and was statistically significant. The study however was small with only 21 patients. In a larger study by Shafti et al (2014) a comparison between Olanzapine and Risperidone Drug-Induced Electrocardiographic Changes was performed. 268 patients were entered into the open arm study for random assignment. The results showed that while 14.86% and 25% of the cases in the olanzapine group showed prolongation and shortening of QTcF, respectively, comparable changes in the risperidone group were restricted to its prolongation (32.5%).
Consistency	There is a level of inconsistency in the overall data package with respect to olanzapine especially from the literature search, with numerous publications showing cases of clear QT prolongation and others showing that there could be a QT interval shortening effect. Further inconsistency arises from the fact that QT interval prolongation is a labelled effect of Olanzapine and well documented in the literature.
Specificity	This data for QT shortening is not available for olanzapine.
Analogy	No anology can be drawn in this case

Overall assessment:

In the Eudravigilance database the association of olanzapine with QT interval shortening was disproportionally reported for this drug over others. Literature review supports the relation but case review does not.