EVOLVEMENT OF EU REGULATIONS ON INNOVATIVE MEDICINES

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To my daughter Elyse

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Abstract

Innovative medicines in the EU must follow regulatory requirements appertaining to the centralised procedure for registration. The study of the evolvement of EU regulations on centrally authorised products (CAPs) could shed light on the impact of the regulations on the access to innovative medicines. The methodology consisted of two parts: 1) A review and an analysis of the use of EU regulatory early access tools including the compilation of a glossary of regulatory terms, 2) An assessment of impact on public health through the non-availability of CAPs, identification of accessibility challenges of innovative medicines, and identification of alternative existing legislative tools to increase access to innovative medicines. Part 1: The early access tools selected for analysis were conditional marketing authorisation (CMA) and marketing authorisation under exceptional circumstances. The glossary compiled defined 280 regulatory terms. The results of the review and analysis have shown that between 2001 and 2016 a total of 65 innovative medicines were centrally authorised using CMA (35) and marketing authorisation under exceptional circumstances (30); 28 given a new active substance status, 33 an orphan designation and 7 withdrawn. Part 2: Between 1995 to 2015 a total of 822 CAPs covering 522 Anatomical Therapeutic Chemical (ATC) Codes were authorised in the EU. The Maltese NHS formulary does not include 322 (61%) of the 522 ATC Codes. Identified challenges with importation of CAPs in Malta are the low volumes required and the costs of the innovative medicines. In 2015-2016, 5 CAPs were imported as unlicensed medicines on a named patient basis and 19 CAPs as exceptional cases according to Article 20 of the Malta Medicines Act to increase access to innovative medicines in Malta. Until 2015, the parallel distribution system was not used to import CAPs in Malta. A one-year pilot project with fee reductions for parallel distribution notifications for CAPs which resulted in the importation of 5 parallel

distributed CAPs, was launched by the European Medicines Agency (EMA) in 2016. Early access tools specified in EU regulations such as CMA and marketing authorisation under exceptional circumstances require more awareness, and intelligent interpretation and application. The pilot parallel distribution project involving notification fee reductions specifically authorised by the EMA specifically for Malta, was beneficial to accessibility of medicines in practice. This study is being used as an example by the European Commission to show that, in the interest of European citizens, flexibility in the regulation is possible, confirming an innovative concept of changing the perception of the EU that regulations are not biased towards safety and efficacy at the detriment of accessibility.

Keywords: Authorisation under exceptional circumstances, conditional marketing authorisation, early access tools, innovative medicines, parallel distribution

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ATC	Anatomical Therapeutic Chemical
CAP	Centrally authorised product
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
CMC	Chemistry, Manufacturing and Control Efficacy
COMP	Committee for Orphan Medicinal Products
CPSU	Central Procurement and Supplies Unit
DCP	Decentralised Procedure
DPA	Directorate of Pharmaceuticals Affairs
EC	European Commission
e-CTD	Electronic Common Technical Document
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
EURORDIS	European Organisation for Rare Diseases
EUPATI	European Patients Academy on Therapeutic Innovation
EVWEB	Eudravigilance website
FDA	Food and Drug Administration
FDASIA	FDA Safety and Innovation Act
GFL	Government Formulary List
GxP	Good Practice
HMA	Heads of Medicines Agencies

HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
INN	Non-proprietary name of medicinal products
MAH	Marketing Authorisation Holder
MAPP	Medicines Adaptive Pathways to Patients
MHLW	Japanese Ministry of Health, Labour and Welfare
MMA	Malta Medicines Authority
MRP	Mutual Recognition Procedure
NHS	National Health Service
OR	Overall Remission Rate
ORR	Objective response Rate
OS	Overall Survival
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PRAC	Pharmacovigilance and Risk Assessment Committee
PRIME	Priority Medicines
PSA	Parallel Scientific Advice
PSUR	Periodic Safety Update Report
RCT	Randomised Controlled Trials
RMP	Risk Management Plan

SAKIGAKE	Ministry Project Team to Lead the World in the Practical Application of Innovative Medical Products
SQL	Structured Query Language
USA	United States of America
USP	United States Pharmacopoeia
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

1.1 Defining innovation

Ongoing debates in the pharmaceutical area on intellectual property (Tomes, 2016), pricing and reimbursement (Eichler et al, 2016; Garattini et al, 2016) and research and development (Khan et al, 2016) have a common factor; the strive towards innovation. There is lack of clarity about the true meaning of innovation, and as a result perplexities regarding the kind of new medicines which should be pursued, protected and encouraged through health policy and clinical practice exist (Morgan et al, 2008).

Innovation is increasingly becoming a major consideration in the valuation of new medicines (Jeffrey et al, 2012). The innovative value of a medicine is an intrinsic property of the new active substance and depends on the therapeutic area for which the medicine is indicated and the availability of medicines to treat the same condition (Caprino & Russo, 2006). In 2008, Aronson defined innovative medicines as medicines which may arise from changes in the properties of the active substance, including chemical structures, synthesis methods and manufacturing processes, pharmaceutical form, pharmacodynamics, pharmacokinetics and other therapeutic properties (Aronson, 2008). In 2009, Kennedy proposed that an innovative medicine must show improvements when compared to existing therapies and there should be an essential change in the outcomes for the patients. In 2012, Aronson et al. proposed a broader definition of pharmaceutical innovation, which includes clinical usefulness, economic aspects and the type of innovation. The degree to which the proposed molecule is really novel should be assessed, taking into consideration that sharing the same characteristics and qualities of another medicine would not be novel. On the other hand, novel use may be discovered for established ‘old’ medicines (Aronson et al, 2012). When considering usefulness, a medicine may be considered innovative when it provides benefit in a

condition for which no effective treatment exists, an improvement to already existing treatment, a safer treatment and a more cost-effective and convenient treatment (Aronson et al, 2012). The proposed definitions by different authors show progress in the disputes on pharmaceutical innovation (Akkari et al, 2016), and suggest a participatory contribution from stakeholders covering the patients, industry, governments and regulatory agencies, to establish an agreement and coordinate research and innovation priorities (Canongia et al, 2004).

1.2 Innovation and Regulation

Medicines regulation started in the 19th century, which laid a solid base for modern drug research and development of the pharmaceutical industry after World War II (Rago and Santoso, 2008). Public health disasters and events have catalysed development of medicines regulation (Callréus and Schneider, 2013). One of the earliest disasters which triggered the need for regulation occurred in 1937, when more than one hundred children in the United States of America (USA) were fatally poisoned by the preparation of an antimicrobial sulphanilamide dissolved in diethylene glycol, a lethal solvent (Avorn, 2012). Events such as the thalidomide disaster which occurred in 1961 (Paine, 2017), and withdrawal of the non-steroidal anti-inflammatory drug rofecoxib (Vioxx®) in 2004 due to safety concerns of an increased risk of cardiovascular events (Collins et al, 2013), stimulated regulatory reforms globally. Systems of medicine assessment of pre-clinical, clinical, and quality data performed by medicines regulatory agencies were established (Lumpkin et al, 2012).

Regulatory science research for determination of product safety was first developed in the early part of the 20th century, and continues to support innovation of the processes needed for regulatory decisions (Jasanoff, 2009; Patel and Miller, 2012).

Regulatory science functions as a bridge for delivery of a drug with related information and knowledge to target patients and society. Three functions of regulatory science include: providing the tools for data production, providing a basis for data assessment and balancing the various factors involved in the decision (Tominga, 2011). Regulatory science enables co-evolution of science, legislation and policies in order to assess benefit-risk assessment throughout the life-cycle of medicines (Per Spindler et al, 2016). It is important to differentiate regulatory science from regulatory affairs, which both focus on complying with regulations. Regulatory affairs involves the application of already defined regulatory principles to a given drug development or drug life cycle in a reactive manner, for example to sociological norms and quality of life. On the other hand, regulatory science proactively analyses regulatory principles and strives to evolve them along the continuity of scientific progress (Callre´us and Schneider, 2013), for example in the context of safety, evidence and personalised medicine. The concept of the bridge between regulatory affairs and regulatory science in line with the views of Tominga (2011) and Callreus and Schneider (2013) was developed in Figure 1.1.

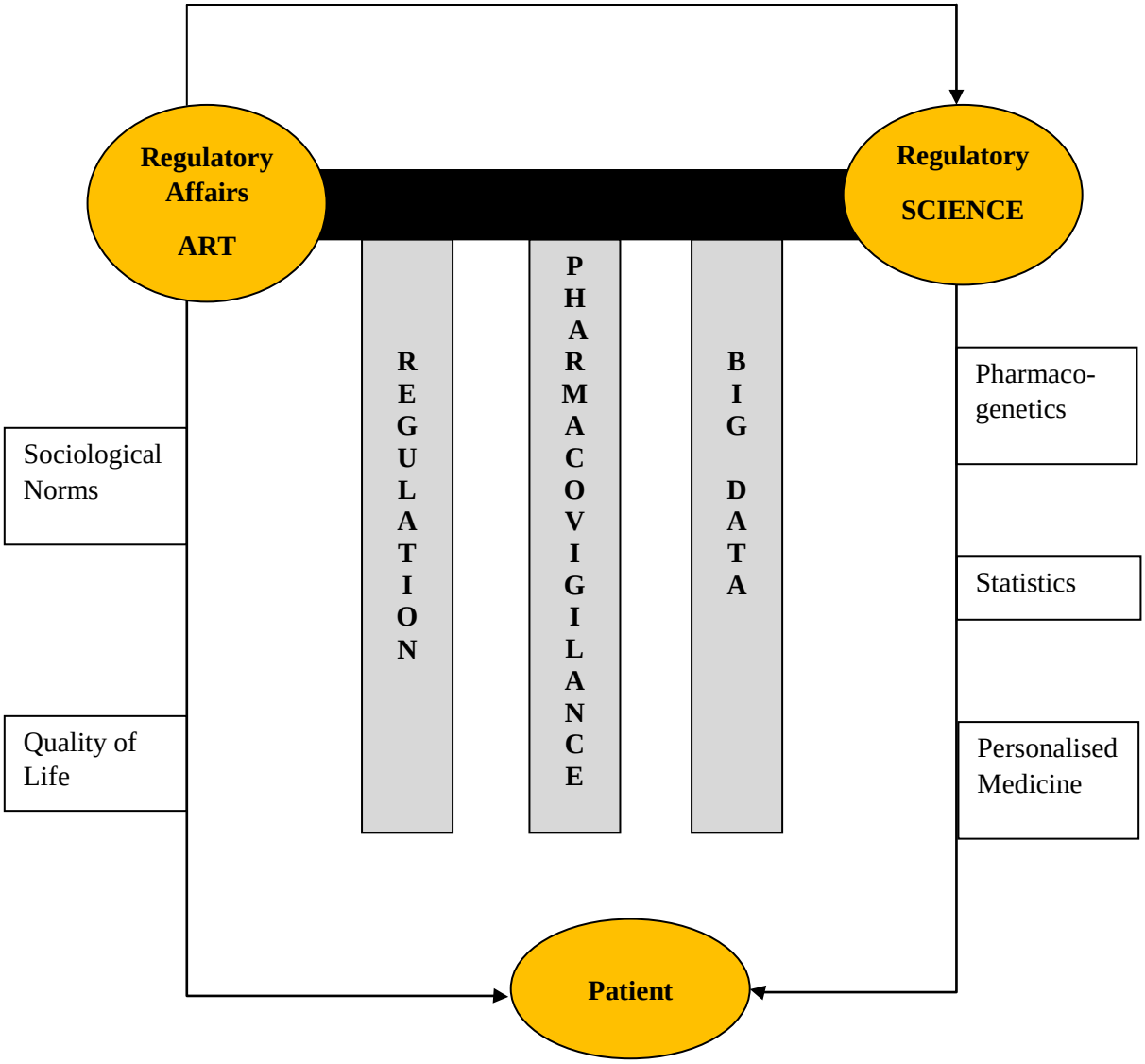

Figure 1.1 The bridge between regulatory affairs and regulatory science

Regulatory science has evolved over the years in the three major drug development regions of the world - Europe, USA and Japan (Milne et al, 2016). Improvement in regulatory science research tools and techniques has demanded a change in how regulatory science research is applied to protect and promote public health (Rago and Santaso, 2008). Understanding how public health disasters have shaped the development of health regulations is necessary for advancing the regulatory concept towards a preventative and proactive framework, and recognising where innovation can facilitate the shift from reactive to proactive policies (Patel and Miller, 2012).

1.2.1 Evolution of Regulatory Science in the European Union

In European countries, major revolution of medicine regulation started after the thalidomide tragedy in 1961. Until the thalidomide tragedy, medicines could be sold upon notification to the health authority and no safety, efficacy or quality data were required to be submitted prior to marketing (Rahalkar, 2012).

Adoption of European Commission (EC) Directive 65/65/EEC of January 26, 1965[1], mandates that a medicine may only be placed on the EU market after a marketing authorisation has been granted by at least one competent authority in Europe. Since 1965, the EU pharmaceutical legislation framework was extended and developed with the aim of protecting public health and preserving free movement of medicines in the EU with the enactment of Directive 2001/83/EC.[2]

In 1995, a new system for authorisation of medicines in the EU was adopted with the establishment of the European Medicines Agency (EMA) (Bauschke, 2011). EMA was founded with a legal mandate to carry out scientific evaluation of marketing authorisation applications, with the EC taking the final decision on granting an EU marketing authorisation (Regnstrom et al, 2010).

[1] European Council. Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products [Online]. Official Journal of the European Union 1965; 022: 0369 - 0373 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31965L0065:EN:HTML

[2] European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2001; L311:67-128 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=EN

Regulations were based on two separate European Community procedures for granting a marketing authorisation for a medicine; namely the centralised procedure[3] and the mutual recognition procedure.[4] The centralised procedure is administered through EMA, and medicines regulatory authorities of member states are responsible for mutual recognition procedure. In addition, a national authorisation for a product that is marketed in only one member state is possible (Kohler, 2011). Directive 2004/27/EC[5] came into force in 2005 providing another option to authorise medicines within the EU through the decentralised procedure.[4]

EMA's remit has expanded over time, in compliance with new EU legislations to evaluate human and veterinary medicines.[6] Responsibilities of EMA were extended to include assessment of medicinal products developed in the specialised areas of medicines for rare diseases in 2000,[7] herbal medicines in 2004,[8] medicines for

[3] European Commission. Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [Online]. Official Journal of the European Union 2014; L136:1-33 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF

[4] European Commission. Volume 2B Notice to Applicants Medicinal products for Human Use – Presentation and Format of the Dossier - Common Technical Document [Online]. Brussels: EC; 2008b [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

[5] European Commission. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2004; L136:34-57 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0027&from=EN

[6] European Medicines Agency (EMA). History of EMA: Milestones and Achievements [Online]. UK: EMA; 2015 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp

[7] European Commission. Regulation No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products [Online]. Official Journal of The European Union 2000; L18:1-5 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

[8] European Commission. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2004; L136:85-90 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2004_24/dir_2004_24_en.pdf

paediatrics in 2006[9] and advanced therapy medicines since 2007.[10] Attaining these responsibilities resulted in the creation of new scientific committees which provide expertise in these areas. With the establishment of the Committee for Orphan Medicinal Products (COMP) in 2000,[6] EMA opened its doors to patients and healthcare professionals**.** Patient and healthcare professional representatives take part in EMA's scientific committees as full members, with unique viewpoints and experiences to discussions, and playing a role in the assessment of risks and benefits of medicines. In 2014, patient representatives discussed the benefit-risk evaluation of a medicine within the Committee for Medicinal Products for Human Use (CHMP) for the first time.[11]

With the establishment of the Pharmacovigilance and Risk Assessment Committee (PRAC) in 2012,[12] EMA started to play a role in monitoring the safety of medicines across Europe, moving towards addressing adherence to regulation of medicines. As of January 2015, EMA has been implementing its landmark policy on publishing clinical data supporting European decision-making on medicines. Publishing clinical data provides an unprecedented level of transparency for patients, healthcare

[9] European Commission. Regulation No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006 [Online]. Official Journal of The European Union 2006; L378:20-21 [cited 2017 May 05]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf

[10] European Commission. Regulation No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products [Online]. Official Journal of The European Union 2007; L324:121-137 [cited 2017 May 05]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394_cons_2012-07/reg_2007_1394_cons_2012-07_en.pdf

[6] European Medicines Agency (EMA). History of EMA: Milestones and Achievements [Online]. UK: EMA; 2015 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp

[11] European Medicines Agency (EMA). EMA activities where patients and consumers are involved [Online]. EMA/652164/2014 UK: EMA; 2014 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179568.pdf

[12] European Commission. Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council [Online]. Official Journal of the European Union 2004; L159:5-25 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

professionals, academia and industry.[5] The principles of compliance, adherence and concordance (De las Cuevas, 2011) were appled to the evolvement of EMA over the years in Figure 1.2.

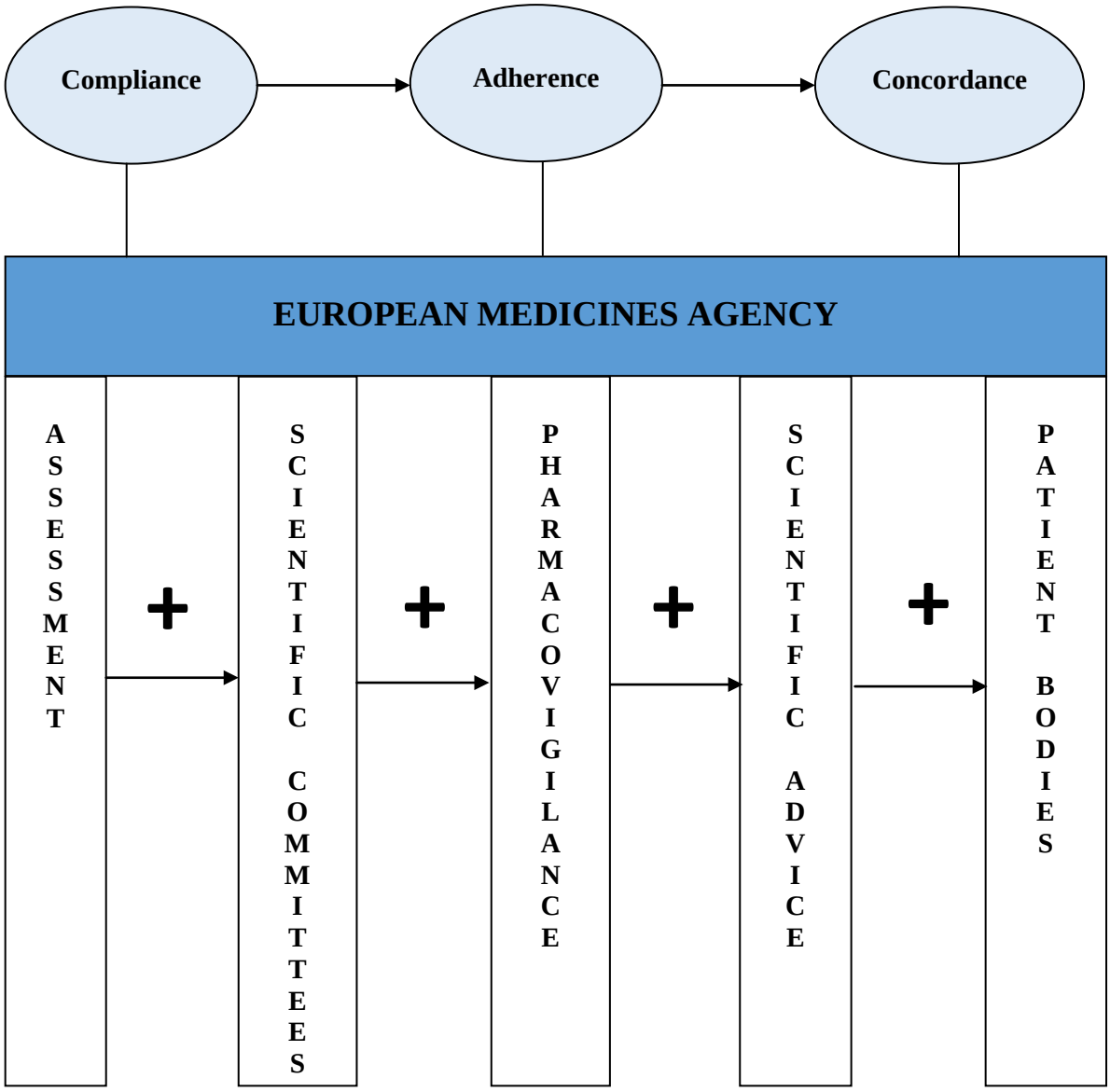

Figure 1.2 **Role of the European Medicines Agency in the progress of regulatory science**

[5] European Commission. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2004; L136:34-57 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0027&from=EN

1.2.2 Evolution of Regulatory Science in the USA

In the USA, the pharmaceutical industry was developed during the Mexican-American war between 1846 and 1848, where importation of falsified medicines for malaria, cholera, dysentery and yellow fever led the federal government to create custom laboratories (Rahalkar, 2012). The first law which controlled importation of medicines was the Import Drugs Act of 1848, which mandated inspection of imported drugs for quality and purity at port entry (Rahalkar, 2012). In 1938, the federal government recognised the United States Pharmacopoeia (USP) as an official compendium to define the quality and purity of drugs (Boring, 1997).

New legislations for medicines control were implemented in 1906 due to multiple tragedies worldwide and this was the time when ancient medicine manufacturing and distribution traditions evolved into a modern, highly organised, and regulated pharmaceutical industry (Rahalkar, 2012). Almost five decades after implementation of the 1848 Import Drugs Act, the vaccines tragedy occurred in 1901, where diphtheria antitoxin and smallpox vaccines were found to be contaminated, resulting in the death of nineteen patients, including fourteen children (London, 2014). The Biologics Control Act of 1902 was enacted following the vaccine tragedy, mandating licensing for the manufacture and distribution of biological products, including serum, vaccines, toxins and viruses, and inclusion of labelling illustrating the manufacturer details, license number, identification of product and expiry date (Marshall and Baylor, 2011). Labelling requirements incorporating the active substances and excipients used for manufacture of the medicine were mandated by the 1906 Food and Drugs Act, also known as the Wiley Act (Janssen, 1981).

The Food and Drugs Act was the starting point for establishment of the Food and Drug Administration (FDA) which was founded in 1930.[13] In 1938, concerns about the safety of medicines were raised following the sulfanilamide elixir tragedy, where more than one hundred people died due to use of diethylene glycol, a highly toxic solvent, for mixing of the sulfanilamide drug (Avorn, 2012). The sulphanilamide tragedy led to enactment of the Food, Drug and Cosmetic Act of 1938, where pre-marketing authorisation of all new drugs, evidence from safety studies and directions for safe use became mandatory (Rahalkar, 2012).

The thalidomide tragedy in Europe endorsed the 1962 Kefauver-Harris Drug Amendments, where evidence of efficacy and greater safety data for new drugs was required to apply for a marketing authorisation (Naci et al, 2012). The need to assess the safety of medicines stimulated growth and development in regulatory science tools and techniques (Patel and Miller, 2012). Despite additional requirements for pre-marketing safety studies in animals and extensive clinical studies in humans, a public health disaster in 2004 occurred with rofecoxib, where the cardiovascular events were too rare to be detected until the product was extensively used in a large population. This incident demonstrates the importance of pharmacovigilance to identify rare and severe adverse events and avert a significant public health disaster (Khan et al, 2006).

In 2010, the FDA started to boost the regulatory science base of its operations which set focus on multidisciplinary themes, and opened avenues for collaboration between medicines authorities, universities, industry, patient groups, and other stakeholders (Fitzgerald, 2011). In 2012, the FDA Safety and Innovation Act (FDASIA) was signed

[13] US Food and Drug Administration. Significant dates in US food and drug law history [Online]. US: FDA; 2014 [cited 2017 May 05]. Available from: URL: https://www.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm

and provided the ‘Breakthrough Therapy Designation’; enabling the FDA to expedite development and review of novel breakthrough medical therapies for serious or life-threatening diseases on preliminary, but satisfactory clinical evidence, while upholding appropriate standards for safety and effectiveness (Sherman et al, 2013).

FDA has long supported regulation of the global marketplace through its early and strong regulatory activity, innovative approaches to developing and advancing regulatory science, and its reputation for conducting state-of-the art regulatory research (Patel and Miller, 2012). The thalidomide tragedy was a landmark that shaped legislation in the USA, fostered development of the current regulatory paradigm for pharmaceuticals and promoted adoption of equivalent regulatory approaches internationally. To meet the demand of promoting and protecting public health in the global context, regulatory science research is being directed towards delivering the benefits of innovative technologies to consumers, while maintaining product safety and quality (Carpenter, 2010). The regulatory paradigm of the FDA, outlined by Patel and Miller (2012), is being transformed from a reactive to a proactive framework (Figure 1.3).

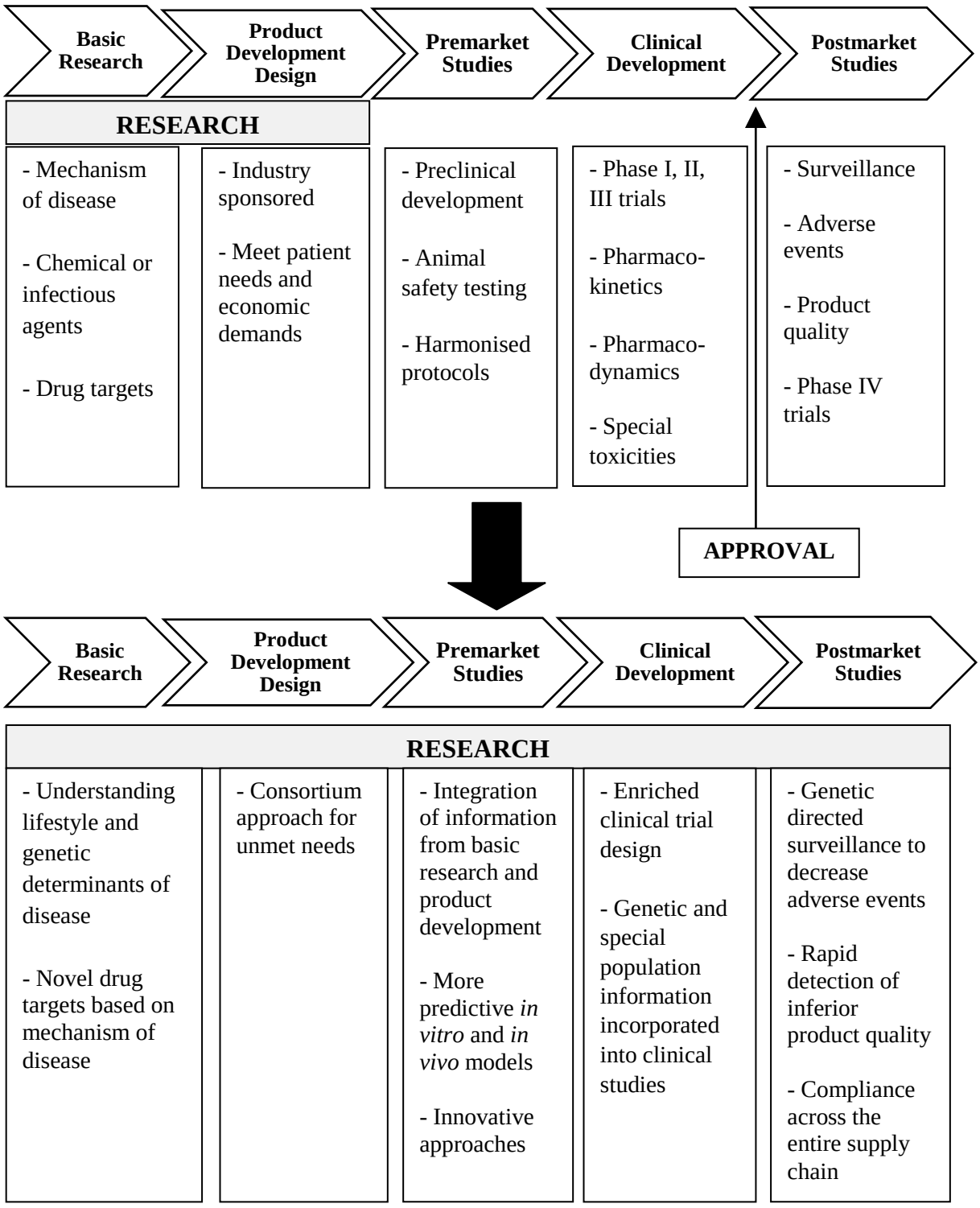

Figure 1.3 Food and Drug Administration regulatory paradigm moving from a reactive to a proactive framework

Reproduced from: Patel M, Miller MA. Impact of regulatory science on global public health. The Kaohsiung Journal of Medical Sciences 2012; 28(7):S5-9.

1.2.3 Evolution of Regulatory Science in Japan

In Japan, regulatory science refers to the science of predicting, evaluating, and determining, fairly and promptly, the quality, safety and efficacy of pharmaceuticals and medical devices based on scientific knowledge (Milne et al, 2016). The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) was established and came into service on April 1, 2004 with the mission to contribute to the improvement of public health (Asahina et al, 2013). The PMDA regulatory science research activity and roles in the medicine regulatory framework are based on a three-pillar system (Figure 1.4).

The PMDA performs scientific consultation and review of regulatory medicine authorisations based on the quality, efficacy, and safety data submitted, where medicines play a key role in the promotion and protection of public health. The PMDA carries out safety measures by collating and evaluating post-marketing data, disseminates reliable information to patients and health care professionals and provides assistance to people experiencing an adverse drug reaction or biological medicine-induced infection.[14]

PMDA defines regulatory science as a science that provides appropriate predictions, evaluations, and judgments to incorporate the outcomes of technology into the most desirable form for people and society.[15]

[14] Pharmaceuticals and Medical Devices Agency (PMDA). Profile of services 2011-2012 [Online]. Japan: PMDA; 2012 [cited 2017 May 05]. Available from: URL: http://www.pmda.go.jp/english/about/pdf/profile_of_services.pdf.

[15] Japanese Ministry of Health, Labour and Welfare (MHLW). Strategy of SAKIGAKE [Online]. Japan: MHLW; 2014 [cited 2017 May 05]. Available from: URL: http://www.mhlw.go.jp/english/policy/healthmedical/pharmaceuticals/dl/140729-01-01.pdf.

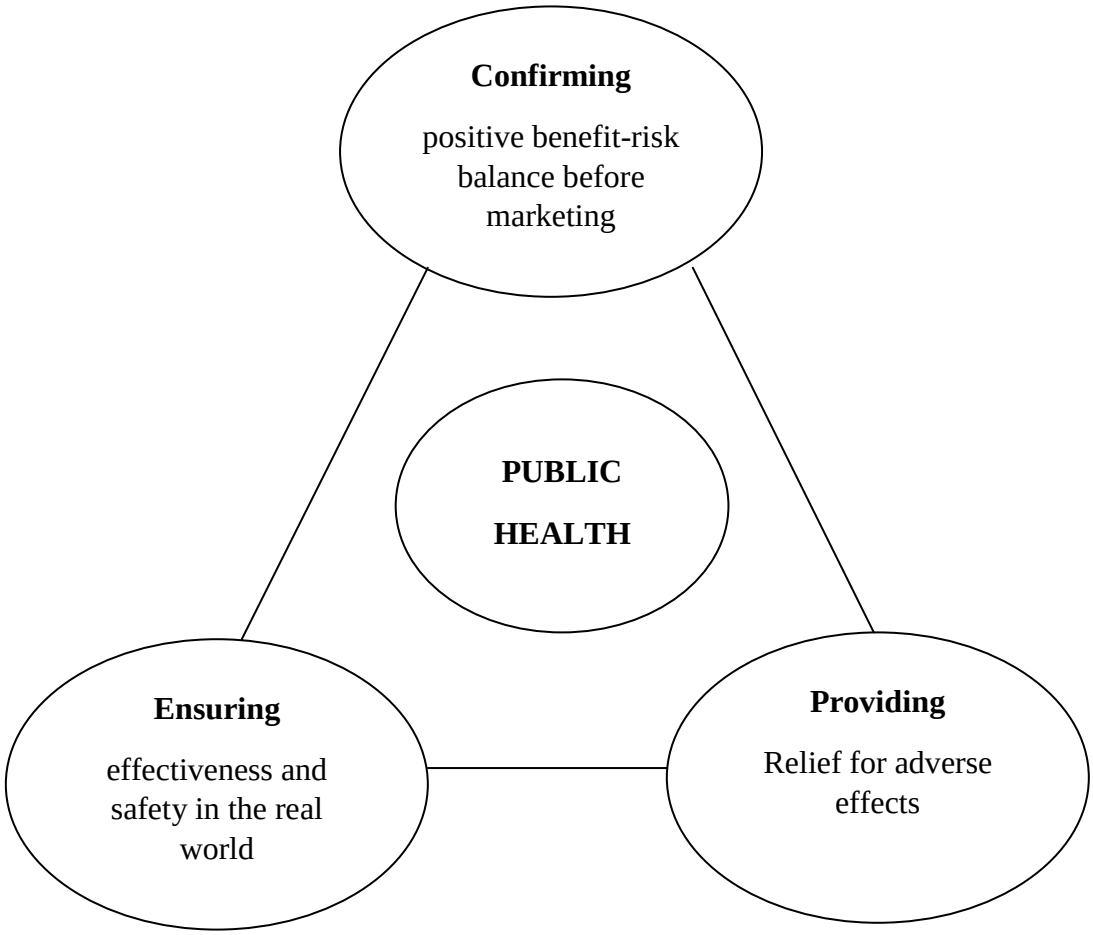

Figure 1.4 The Japanese Pharmaceuticals and Medical Devices Agency 3-pillar system for public health

Reproduced from: Asahina Y, Tanaka A, Uyama Y, Kuramochi K, Maruyama H. The roles of regulatory science research in drug development at the pharmaceuticals and medical devices agency of Japan. Therapeutic Innovation and Regulatory Science 2013; 47(1):19-22.

In 2010, the Regulatory Science Research Division of the PMDA was established with the aim of enhancing the transparency of the agency's decision-making policy and strengthening in-house research activities on regulatory science (Tominaga et al, 2011; Asahina et al, 2013). The Japanese Ministry of Health, Labour and Welfare (MHLW) secured funding for collaborative projects in regulatory science. One of the collaborative projects was established in 2014 with the Ministry Project Team to Lead the World in the Practical Application of Innovative Medical Products (SAKIGAKE), where a team was selected to address specific policies of the MHLW, such as promotion

of research and development and of regulatory science, and aspects of regulatory reviews and external collaborations (Spindler, 2016).

1.3 Medicines Regulatory Systems for Innovative Medicines

The regulatory perspective for innovative medicines is to protect public health (Rago and Santoso, 2008), and it is important that the aim of safeguarding public health is achieved by means that do not hinder the development of innovative medicines. The necessity to have innovative medicines on the market earlier, especially for life-threatening diseases, and where there is an unmet medical need, is a challenge to improve medicines regulatory systems (Ormarsdottir et al, 2008).

1.3.1 Challenges for the Medicines Regulatory System

A key challenge for the medicines regulatory system is to maintain its efficiency to ensure that a continuous flow of innovative and required medicines enter the market in a timely manner (Carpenter et al, 2005; Miller et al, 2007). Trends indicate that research and development expenditures have increased, however there has been no increase in the number of newly developed medicines submitted to regulatory agencies (Paul et al, 2010; Khanna, 2012). According to pharmaceutical companies, one of the reasons for the decrease in drug development is due to overcautious regulators, leading to increased research and development expenditures and lengthy medicine development timelines (Scannell et al, 2012).

Medicines innovation in the 21st century is markedly different from medicines innovation of the 20th century, when more complex answers about the effects of a medicine are demanded by both the regulatoes and the community. Long-term effectiveness and safety data, along with attention to quality of life and cost issues and comparative effectiveness, continue to gain greater prominence (Lumpkin 2012).

Regulators have to find an appropriate balance between the need to ensure that decision-making is based on scientifically valid data and the need for access to new medicines (Eichler et al, 2008). A balance between the evidence of efficacy and safety, with its inherent uncertainties, and consideration for the need of 'improved' medicines to treat the condition is important.[16] Medicines regulatory agencies have been criticised for being exceedingly tolerant on risks or for being overly averse on presenting risks. A drive towards an excessive focus on avoiding risks and uncertainties affect patients by creating a delay in accessing medicines and lost therapeutic options. Medicine regulation maximises benefits in public health and minimises risks (Eichler et al, 2013). Excessive risk-tolerance is not in the interest of public health since ineffective or unsafe drugs will be allowed to be placed on the market (Figure 1.5). On the other hand, excessive risk-aversion can result in patients being denied potentially useful treatments (Eichler et al, 2013).

[16]European Medicines Agency (EMA). Road map to 2015: The European Medicines Agency's contribution to science, medicines and health EMA/299895/2009 [Online]. UK: EMA; 2010 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf

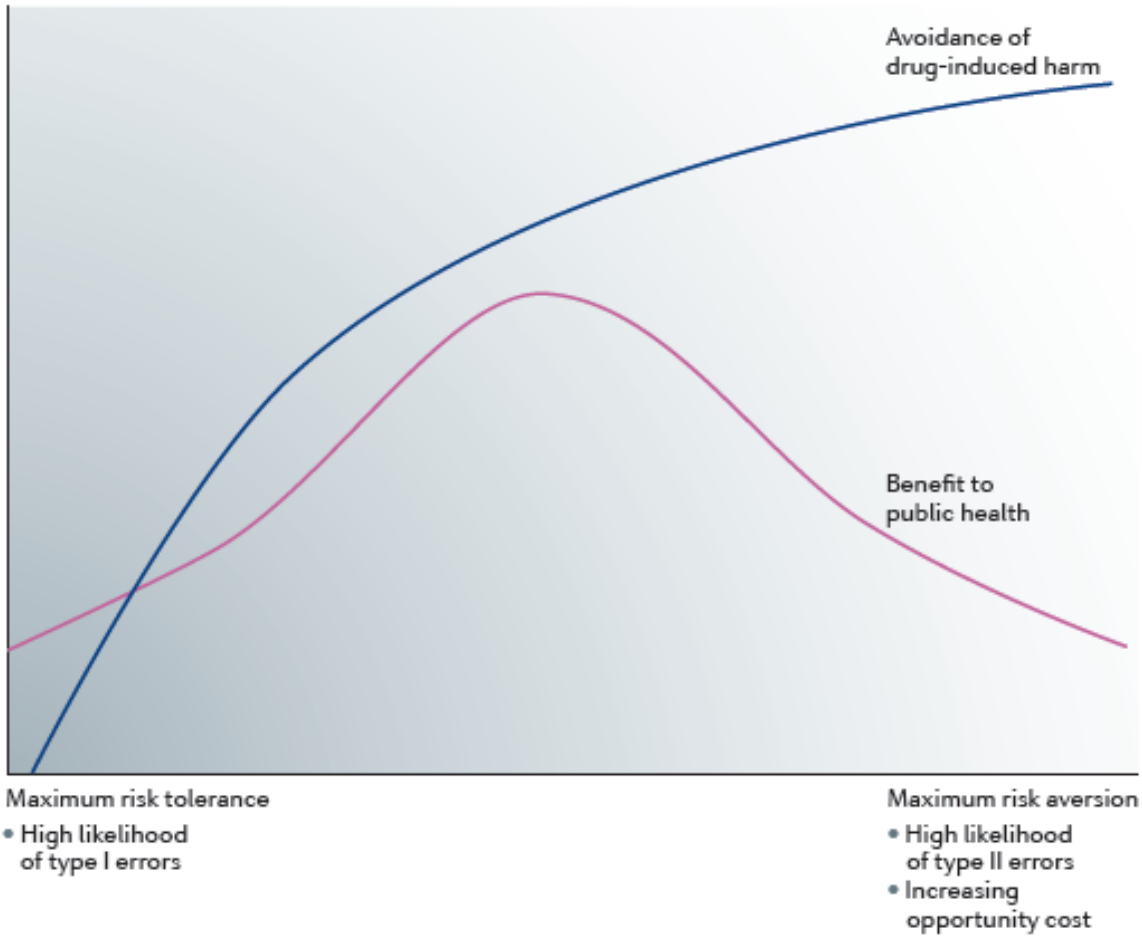

Figure 1.5 Public health benefits versus risk aversion in medicine regulation

This graph shows the relationship between risk tolerance and risk aversion by regulators on the x-axis, and the expected outcomes in terms of avoidance of medicine induced patient harm (blue line) or public health gains (purple line) on the y-axis.

Reproduced from: Eichler HG, Bloechl-Daum B, Brasseur D, Breckenridge A, Leufkens H, Raine J, et al. The risks of risk aversion in drug regulation. Nature Review Drug Discovery 2013; 12(12):907-16.

The need to balance early market access and the need for comprehensive benefit-risk information are becoming the regulators' dilemma (Table 1.1). All these factors influence, or seek to influence, the timing of marketing authorisation, which determine the time at which patients gain access to new medicinal products (Wirthumer-Hoche and Bloechl, 2016).

Table 1.1 The Regulators' Dilemma

Request for shorter timelines with higher level of uncertainty	**Need for more or larger studies with delayed market access**
Industry	*Payers, prescribers and Health Technology Assessment (HTA) assessors*
Require favourable conditions for innovation	Request comparative efficacy and effectiveness data
Patients and carers	*Media and the scientific community*
Demand early access to potentially life-saving medicines	Demand more thorough safety assessment after repeated market withdrawals
Unmet medical needs (examples)	*Excess medicalisation*
Ageing populations, epidemiology of obesity, diabetes	Obesity, metabolic syndrome, mood disorders

Reproduced from: Wirthumer-Hoche C, Bloechl-Daum B. Current issues in drug regulation. In: Müller M. Clinical pharmacology: Current topics and case studies. 2nd ed. Switzerland: Springer International Publishing; 2016. p19-31.

Another key challenge for the medicines regulatory system, as described by Light and Lexchin (2012), is to ensure that the medicinal products developed are those which are required most by society. The 2013 Priority Medicines Report (Kaplan et al, 2013) demonstrated that for highly prevalent disease areas, such as some infectious, central nervous system, cardiovascular and tropical diseases, as well as for many rare diseases, new or more appropriate treatments are needed. Although regulatory agencies do not set the research agenda of pharmaceutical companies, they can stimulate drug development for such diseases, by for example facilitating the approval process (Putziest, 2013).

1.3.2 Marketing Authorisation Dossier

Medicine regulation and decision-making by regulatory authorities is largely based on experience gained from the successive dossiers. Regulatory guidelines and scientific advice in relation to the life-cycle of a medicine are based on the knowledge obtained from the marketing authorisation dossiers. Determinants for successful licensing are a positive and relevant clinical outcome in phase III studies, which can be understood from thoroughly planned phase II studies with mode of action, proof of concept, and dose finding data. Irrespective of whether the drug is an orphan drug or other, skipping the 'learning phase' is counter-productive to the licensing process (Putzeist et al, 2012a; Putzeist et al, 2012b). Eichler et al (2008) highlighted a decrease in non-approval rates of new active substances. Understanding whether non-approval of new active substances was due to failed drugs or failed drug development plans would be decisive. A lack of randomised clinical trials was reported to be a major cause of non-approval (Pignatti et al, 2002).

There is a need for experimental studies to understand the way regulatory authorities evaluate benefits and risks and take approval decisions to further improve the marketing authorisation system (Eichler et al, 2008). It is important to observe determining factors for marketing approval all throughout the cycle of drug development, including the company's drug development plan, pre-clinical studies in the exploratory development phase and confirmatory clinical phase III studies, clinical efficacy and safety outcomes of the confirmatory studies, and medical needs (Putzeist, 2013).

1.3.3 Active control comparisons

Randomised controlled trials (RCT) of drug effects against placebo are key to clinical development of medicinal products. Since the streptomycin trials for tuberculosis in the late 1940s, these trials have been accepted as the paradigm to show evidence of drug efficacy (Ruberg, 2016). Over the years, various modifications in design and analysis of placebo comparisons have been developed. Placebo controls are not always possible and active controls comparisons are required by regulators in order to provide insight on the behaviour of the product compared to standard treatment (Glickman, 2009).

Challenges with active control comparisons exist with respect to issues such as assay sensitivity and choice of control, and are currently not always provided in the marketing application dossier. CHMP is increasingly making requests for data from head-to-head comparisons and has stimulated a debate on when such studies are justified, needed and feasible.[17] Apart from addressing the question of relative efficacy and effectiveness, active control comparisons have provided a wealth of advanced learning on 'old drugs' such as methotrexate in rheumatoid arthritis, beta-blockers in the treatment of hypertension or metformin for diabetes type II (Leufkens et al, 2011).

1.3.4 Application for new indications

As described by Leufkens et al (2011), drug development encompasses a wide range of activities from designing complete new molecules for unmet medical needs, incremental

[17] Committee for Medicinal Products for Human Use (CHMP). Reflection Paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available [Online]. UK:EMA; 2010 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document/01/WC500100710.pdf

change and improvement of existing products, to changes in the target of a medical product during clinical development or post-marketing of an initial application.

Innovation pathways can be used after medicinal products have been initially authorised and used in clinical practice. As outlined by Gelijns et al (1998), innovation pathways can be:

1. A new basic-science investigation which clarifies the mechanisms of action of a certain technology thus encouraging inspiration for new applications
2. Translational research which identifies new uses of technology, either in the laboratory or at the bedside
3. Post-marketing clinical observations about previously unrecognised uses of the technology.

Indications for use of medicines have evolved over time. For decades, aspirin was approved as an inflammatory painkiller, however over the years other indications in the cardiovascular and neurological field were approved (Patrono and Rocca, 2009). Thalidomide was originally developed for insomnia in the late 1950s and was found to cause dramatic birth defects after authorisation (Annas and Elias, 1999). On 24 January 2008, the CHMP issued a positive opinion for a marketing authorisation of thalidomide to be used to treat multiple myeloma in combination with melphalan and prednisone. Since thalidomide was well-known to cause birth defects, several measures were taken to minimise the risk of exposure to unborn children. The CHMP concluded that the benefits of thalidomide outweighed its risks for the treatment of multiple myeloma,

provided that robust measures were implemented to avoid exposure of unborn children.[18]

Applications for new indications have become one of the mainstays of clinical development of medicinal products, a feature that is also related to the multi-target nature of today's therapeutic molecules (Leufkens et al, 2011). While critics of the pharmaceutical industry dispute against 'drugs looking for a disease', it has become understandable that an aspect of the pharmaceutical development lies in the course of applications for new indications offering ample opportunity for knowledge building and learning about the various properties of a medicine (Leufkens et al, 2011).

1.3.5 Risk management plans

Since November 2005, EU Risk Management Plan (EU-RMP) has become an integral part of a marketing application for all new chemical entities in the EU. Moreover, RMPs can be required as part of an application for a new indication. In EU-RMP, the safety profile of the medicine must be summarised and critical safety issues must be specified to plan for pharmacovigilance activities proactively, once the product is approved and used in clinical practice. This pharmacovigilance model intends to produce a shift from a reactive, passive mode of risk management to a more proactive, planned and science-based approach (Borg et al, 2011).

[18] European Public Assessment Report (EPAR). Thalidomide Celgene. EPAR Summary for the public. EMEA/176582/2008 [Online]. UK: EMA; 2008 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/000823/WC500037054.pdf

With a strong focus on the possible harms of a medicinal product, but with an opportunity to learn more about the full profile of the medicinal product, RMPs seem to have a broader scope of development than the initial safety objective for which they were developed (Giezen et al, 2009).

1.4 Facilitating patient access to medicines

The process for successfully obtaining a marketing authorisation for a new medicine is challenging, with an estimated success rate between 1 in 5000 to 1 in 10000 molecules (Rasi and Bonini, 2015). When marketing authorisation is obtained, health technology assessment (HTA) and decisions on pricing and reimbursement often delay access to medicines for patients at national and regional level. This is likely to worsen in the future due to increasing drug costs, particularly for biological agents.[19] An example is the drug ivacaftor, marketed as Kalydeco™. Ivacaftor modifies impairment of the cystic fibrosis transmembrane conductance regulator caused by the mutation G551D in its gene, where glycine in position 551 is replaced by aspartic acid (Condren and Bradshaw, 2013). This mutation is present in 4% to 5% of cystic fibrosis patients and blocks chloride ion access into epithelial cells resulting in production of sticky mucus typical of the disease. Ivacaftor was designated as an orphan drug and showed a marked effect on the forced expiratory volume in one second compared to placebo. It obtained marketing authorisation by both the US FDA and EMA in 2012, only four years after presentation of the dossier to EMA. Unfortunately, due to its high cost, the drug was only available for patients in less than half of European countries in 2014 and it is still undergoing HTA in several countries (Whiting et al, 2014; Ronan et al, 2015). Early

[19]World Health Organisation (WHO). Access to new medicines in Europe: echnical review of policy initiatives and opportunities for collaboration and research [Online]. Geneva: WHO; 2015 [cited 2017 May 05] Available from: URL: http://apps.who.int/medicinedocs/documents/s21793en/s21793en.pdf

dialogue between regulators and HTA-bodies, without limiting the independence of local authorities to take decisions about reimbursement policies, may help in evaluating whether the risks and benefits of a new medicine are associated with the efficient use of resources at an early stage (Rasi and Bonnini, 2015).

1.4.1 Access to medicines through the Maltese National Health Service

In Malta, patients are entitled to free medicines according to Social Security Act Chapter 318[20] and the Fifth Schedule of the same Act.[20] Entitlement is based solely upon the presence of disease and is irrespective of means, income or age. Any patient suffering from any one (or more) of the listed conditions, is entitled to free treatment, available on the Government Formulary List (GFL), for a specific disease. Patients are entitled to free treatment available on the GFL and entitlement is provided according to the GFL policies.

Free medicines entitlement may also occur via the Second Schedule of the Social Security Act, that is, Pink Card for the means tested population. Pink Card holders are only entitled to 'pink positive' items according to the GFL. Pink Card Positive refers to the medicinal products, together with the accompanying prescribing criteria, which can be issued to patients in possession of a Pink Card (Schedule II Card) for conditions not covered by Schedule V of the Social Security Act. Pink Card Positive medicines are classified as items for acute use where treatment should have a rapid onset and is of short duration; items for chronic use if utilised for the treatment of an ongoing or recurring condition; and items for both acute and chronic use according to the condition.

[20] Ministry for Justice, Culture and Local Government. Chapter 318 Social Security Act [Online]. Malta: The Ministry; 1987: 1-162 [cited 2017 May 05]. Available from: URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8794

The Directorate of Pharmaceutical Affairs (DPA), a government entity which falls within the remit of the Ministry for Health, is responsible for the maintenance and update of the GFL. The GFL consists of the non-proprietary name of the medicinal products (INN), dosage form and dosage strength, disease category and Anatomical Therapeutic Chemical (ATC) code. The list contains further information such as prescriber criteria, that is, the category of physicians who are entitled to prescribe a particular medicine, the specific department for which a medicine is being procured, and the pink card positive, that is, the entitlement to a particular medicine, for those patients holding a pink card. A medicine protocol is attached to a medicinal product, restricting its use within the NHS. The protocol is written in a defined format and stipulates the use of such a medicine.

1.4.2 Current issues in reimbursement of medicines

Reimbursing pharmaceuticals is considered an important aspect of healthcare delivery for the state, independent, non-profit statutory institutions, and private health insurance providers (Bucsics, 2010). Reimbursement of pharmaceuticals deals with a range of ethical, social, economic and scientific questions (Kelley et al, 2012; Bauchner, 2016) such as how the price of a new medicine should be determined and by whom, what should be taken into account to determine the value of new medicines, which medicines should be excluded from reimbursement, which is the most equitable type of co-payment, and whether or not to take the economic contribution of the local pharmaceutical industry into account with regard to reimbursement decisions.

During the assessment of the marketing authorisation application of a medicine, the benefit-risk balance is evaluated. Only medicines with positive benefit-risk balance obtain authorisation and can be made available to patients for treatment of the approved indication, or to be used off label at the physician's discretion. In Europe, once marketing authorisation is obtained, country-specific criteria are applied to decide whether medicines will be reimbursed within national health care systems and to set prices of medicines; these criteria vary between relative effectiveness analysis, such as in France and Germany, cost-effectiveness analysis, such as in the United Kingdom and other methods (Leyens et al, 2015).

1.4.3 Convergence of regulatory benefit-risk and economical health technology assessment

Reimbursement and price decisions determine patient access to medicines (Panteli et al, 2015). The net benefit or the added benefit of a medicine has become more relevant than the regulators' evaluation of the benefit-risk balance for the price and reimbursement decision. A quantitative estimate of a new medicine's advantage in comparison with other pharmacological treatment options is also required for a medicine to be reimbursed (Trusk, 2011).

Non-inferiority to a generally accepted comparator is sufficient for a marketing authorisation. The non-inferiority will not justify higher costs when compared to the comparator since it will not be economically-attractive for patients (Eichler et al, 2010). A resulting low price of the medicine may even make the Marketing Authorisation Holder (MAH) decide not to market the comparator. For justification of a higher price,

HTA-bodies and payers will require sound evidence of an additional benefit, preferably from a head-to-head comparison with an appropriate comparator.[21] Trials designed to fulfil the expectations of both regulators and HTA-bodies are in the best interest of both patients and the pharmaceutical industry, avoiding duplication of work and accelerating patient access to medicines by early decisions on price and reimbursement (Leyens and Brand, 2016).

Since 2010, EMA's provision of scientific advice in parallel with HTA-bodies has become an important driver for the convergence of the requirements of European regulators and HTA-bodies. This procedure not only narrows the gap between regulators and HTA bodies' expectations but also promotes harmonisation between positions of the multitude of European HTA-bodies. The benefit-risk balance of a medicine will depend predominantly or exclusively on the medicines' benefits, adverse effects, pharmacological and toxicological effects, which will be the same in different regions of Europe.[22] When HTA-bodies include issues of social context, economic situation and availability of other treatment options into their evaluation, the results must be expected to differ. In parallel, scientific advice procedures, at least a partial harmonisation and an improved transparency and predictability can be achieved.[23]

[21] World Health Organization (WHO). Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Denmark: WHO; 2015 [cited 2017 May 05]. Available from: URL: http://www.euro.who.int/__data/assets/pdf_file/0008/306179/Access-new-medicines-TR-PIO-collaboration-research.pdf?ua=1

[22] European Medicines Agency (EMA). Parallel scientific advice from regulators and health-technology-assessment bodies [Online]. UK: EMA; 2017 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000156.jsp&mid=WC0b01ac0580a11c96

[23] European Medicines Agency (EMA). Best practice guidance for the parallel regulatory – HTA scientific advice procedure EMA/502692/2015 [Online]. UK: EMA; 2016 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500203944.pdf

1.5 Aim and Objectives

The aim of this research was to study the impact of European Union (EU) regulation on access to innovative medicines by analysing authorisation procedures.

The objectives were to:

- Review available EU early access tools to facilitate timely access of innovative medicines to patients in Europe
- Compile a glossary of regulatory terminology for use in a pharmaceutical and academic setting
- Analyse early access tools to understand how clinical studies have been used to obtain a positive outcome during evaluation of medicinal products
- Assess the impact on public health through the non-availability of centrally authorised products in Malta
- Identify accessibility challenges of innovative medicines in Malta
- Identify alternative existing legislative tools to increase access to innovative medicines in Malta.

CHAPTER 2

METHODOLOGY

The methodology chapter covers the:

1. Systematic review of European regulations on the authorisation processes of innovative medicines
2. Identification of available early access tools to facilitate timely access of innovative medicines to patients in Europe
3. Compilation and validation of a glossary of regulatory terms to be used in a pharmaceutical and academic setting
4. Analysis of early access tools to understand how clinical studies have been used to obtain a positive outcome during evaluation of medicinal products
5. Investigation on accessibility of innovative medicines products through the Maltese NHS and exploration of existing legislative tools to increase accessibility of innovative medicines in Malta.

2.1 Authorisation processes of innovative medicines

Systematic review of the European regulations on the authorisation processes of innovative medicines was carried out through the review of Directives and regulations of the EU obtained from the Official Journal of the EU using EudraLex.[24] EudraLex is the collection of rules and regulations governing medicinal products for human use and veterinary use. EudraLex consists of 10 volumes, of which only Volume 1 concerning medicinal products for human use, and Volume 5 concerning medicinal products for veterinary use, present official legislation. The basic legislation is supported by a series of guidelines that are published in the other eight volumes.

[24] European Commission. EudraBook V1 - May 2015 / EudraLex V30 – January 2015 [Online]. Brussels: European Commission; 2015 [cited 2017 May 05]. Available from: URL: https://ec.europa.eu/health/documents/eudralex_en

Regulatory early access tools used to facilitate timely access of innovative medicines to patients in the EU were identified through review of:

1. EMA initiatives launched over the years to facilitate access of innovative medicines to patients. Identification of early access tools was performed through analysis of the EMA website.[25]
2. Scientific articles on regulatory early access tools used in the EU for timely access of innovative medicines to patients. Articles were searched using PubMed®[26] database and Google Scholar[27] literature library. The full texts were extracted from the HyDi Hybrid Discovery[28] search gateway of the University of Malta. Keywords for the search included: Accelerated assessment; adaptive licensing; conditional marketing authorisation; early access tools; early market access; exceptional marketing authorisation; fast-track medicines; innovative medicines; novel therapies; orphan medicines; pharmaceutical innovation; regulatory review time; and unmet medical need.

[25] European Medicines Agency (EMA). EMA website [Online]. UK: EMA; 2017 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001772.jsp&mid=WC0b01ac0580b18a39

[26] U.S. National Library of Medicine. PubMed Database [Online]. Bethesda: USA; 2017 [cited 2017 May 05]. Available from: URL: https://www.ncbi.nlm.nih.gov/pubmed/

[27] Google. Google Scholar [Online]. California: USA; 2017 [cited 2017 May 05]. Available from: URL: https://scholar.google.com/

[28] University of Malta (UOM). HyDi Hybrid Discovery [Online]. Malta: UOM; 2017 [cited 2017 May 05]. Available from: URL: https://www.um.edu.mt/library/hydi/libweb/action/search.do

2.2 Compilation and validation of a glossary of regulatory terms

A literature review was carried out to identify commonly used terms in the pharmaceutical regulatory field. Regulatory terms were identified and defined from the following sources:

1. Directives and regulation of the EU obtained from the Official Journal of the European Union using EudraLex.[24]
2. Review of regulatory information on human medicines available on the EMA website.[25]
3. Review of regulatory information on human medicines available on the Heads of Medicines Agencies (HMA) website.[29]
4. Review of International Conference on Harmonisation (ICH) guidelines available on the ICH website.[30]

A panel of five regulatory affairs experts, two pharmacists and a layperson was recruited to validate the glossary. Feedback received from the panel was used to update the glossary and the completed glossary was printed.

[24] European Commission. EudraBook V1 - May 2015 / EudraLex V30 – January 2015 [Online]. Brussels: European Commission; 2015 [cited 2017 May 05]. Available from: URL: https://ec.europa.eu/health/documents/eudralex_en

[25] European Medicines Agency (EMA). EMA website [Online]. UK: EMA; 2017 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001772.jsp&mid=WC0b01ac0580b18a39

[29] Heads of Medicines Agencies (HMA). HMA website [Online]. HMA; 2017 [cited 2017 May 05]. Available from: URL: http://www.hma.eu/humanmedicines.html?&L=0

[30] International Conference on Harmonisation. ICH website [Online]. Geneva; ICH; 2017 [cited 2017 May 05]. Available from: URL: http://www.ich.org/products/guidelines.html

2.3 Analysis of early access tools

The two early access tools used for the authorisation of innovative medicines, with incomplete comprehensive data at application submission, were selected for in-depth analysis.

A comparative analysis of the two selected early access tools was carried out as follows:

1. Medicinal products granted a conditional marketing authorisation (CMA) or authorisation under exceptional circumstances through the centralised procedure in the EU from January 2001 to December 2016 were extracted from the EMA database.The EMA database includes all centrally approved medicinal products for human use.

2. A comparative review of product characteristics and clinical studies used during drug development was carried out. Descriptive statistics of the product characteristics were reported using Microsoft Excel® 2007.The European Public Assessment Reports (EPAR)[31]available on the EMA website were used as the data source for the following product characteristics:
   a) Overview of authorisations granted by year of authorisation and current status (active/withdrawn)
   b) Stage of procedure when conditional or exceptional authorisation was first considered

[31] European Medicines Agency (EMA). European Public Assessment Report [Online]. UK: EMA; 2017 [cited on 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

c) Average duration of assessment by stage of when conditional and exceptional marketing authorisation were first considered

d) Active Substance

e) Therapeutic area and Pharmacotherapeutic group

f) ATC Code

g) Use of Scientific advice / Protocol assistance

h) New active substance status

i) Orphan Designation

3. Clinical studies during the drug development programme to support a positive outcome during the evaluation by CHMP were identified. The EPARs[32] available on the EMA website were used as the data source for the following pivotal clinical studies characteristics:

a) Phases of pivotal clinical studies

b) Distribution of pivotal studies by phase according to the therapeutic area

c) Study designs including use ofsingle/multiple arms, randomisation, blinding

d) Study designs used according to the therapeutic area

e) Sample sizes used in main/pivotal clinical studies

f) Categorisation of primary endpointsused in thepivotal studies as defined in the study protocol

g) Type of primary endpoints used according to therapeutic area

h) Licensing status of exceptional marketing authorisations

[32] European Medicines Agency (EMA). European Public Assessment Report [Online]. UK: EMA; 2017 [cited on 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

i) Categorisation and status of imposed specific obligations by CHMP to applicants.

4. Comparative overview of the clinical studies used over time according to therapeutic area for medicinal products granted a CMAor authorisation under exceptional circumstances using clinical development programmes.

5. Medicines that were filed for approval but were refused authorisation by the EMA or EC were excluded.

2.4 Review of innovative medicines in Malta

A comprehensive review of the EU and Maltese regulatory systems and the Maltese NHS was carried out to identify existing legislative tools used to optimise access of CAPs in Malta. The applicable regulations, guidelines were identified from the 1) Malta Medicines Authority (MMA) website,[33] 2) Ministry for Health website,[34] 3) Laws of Malta website,[35] 4) Directives and regulations of the EU extracted from the Official Journal of the EU using EudraLex.[24]

[24] European Commission. EudraBook V1 - May 2015 / EudraLex V30 – January 2015 [Online]. Brussels: European Commission; 2015 [cited 2017 May 05]. Available from: URL: https://ec.europa.eu/health/documents/eudralex_en

[33] Malta Medicines Authority (MMA). Malta Medicines Authority website [Online]. Malta: MMA; 2017 [cited 2017 May 05] Available from: URL: http://www.medicinesauthority.gov.mt/home?l=1

[34] Ministry for Health. Ministry for Health website [Online]. Malta: Ministry for Health; 2017 [cited 2017 May 05]. Available from: URL: http://health.gov.mt/en/Pages/health.aspx

[35] Ministry for Justice, Culture and Local Government. Laws of Malta [Online]. Malta: Ministry for Justice, Culture and Local Government; 2017 [cited 2017 May 05] Available from: URL: http://www.justiceservices.gov.mt/

2.4.1 Determination of therapeutic coverage of centrally authorised products in Malta

A gap analysis was carried out to determine the therapeutic coverage of CAPs in Malta. The list of authorised CAPs, list of authorised medicinal products in Malta and list of medicinal products available through the Maltese NHS were the data used for the gap analysis.

2.4.1.1 Medicines authorised through the centralised procedure

A list of CAPs was retrieved from the EMA website.[36] The list included CAPs authorised from October 1995 to May 2015. All centrally authorised products were analysed and relevant information was compiled using Microsoft Excel® 2007. The following data was captured: 1) Medicine name, 2) Product reference number, 3) Active ingredient, 4) Common name, 5) ATC code, 6) Authorisation date, and 7) Indication.

The ATC classification system[37] was used to classify the captured indications. Each bottom-level ATC code stands for a pharmaceutically-used substance, or a combination of substances, in a single indication or use. With this coding system, one medicine can have more than one ATC code. The full code consists of 5 characters (Table 2.1):

[36] European Medicines Agency (EMA). Centrally Authorised Products for Human Use Online Database [Online]. UK: EMA; 2015 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&startLetter=View+all&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=generics

[37] WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015 [Online]. Norway: Norwegian Institute of Public Health; 2015 [cited 2017 May 05]. Available from: URL: https://www.whocc.no/atc_ddd_index/

1. The first level is the anatomical area denoted by a single letter, for example G for ‘Genito Urinary System and Sex Hormones’.
2. The second level is the therapeutic subgroup area denoted by two digits, for example G03 which corresponds to ‘Sex Hormones and Modulators of the Genital System’.
3. The third level is the pharmacological subgroup denoted by a single letter, for example G03G which corresponds to ‘Gonadotropins and other Ovulation Stimulants’.
4. The fourth level is the chemical subgroup denoted by another single letter, for example G03GA which corresponds to Gonadotropins.
5. The fifth level or bottom level corresponds to a chemical substance or combination of substances denoted by two digits.

Table 2.1 Structure of the coding system as illustrated by the complete classification of follitropin alfa

Code	Description	Level description
G	Genito Urinary System and Sex Hormones’	1st level –Anatomical main group
G03	Sex Hormones and Modulators of the Genital System	2nd level –Therapeutic subgroup
G03G	Gonadotropins and other Ovulation Stimulants’	3rd level – Pharmacological subgroup
G03GA	Gonadotropins	4th level – Chemical subgroup
G03GA05	Follitropin alfa	5th level – Chemical substance

Adapted from: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015 [Online]. Norway: Norwegian Institute of Public Health; 2015 [cited 2017 May 05]. Available from: URL: https://www.whocc.no/atc_ddd_index/

All indications per CAP were subsequently analysed in order to associate an ATC code. Second level ATC codes were used to assess the therapeutic coverage.

2.4.1.2 Authorised medicinal products in Malta

The Malta Medicines List[38] published on the MMA website was used as the data source. The Malta Medicines List includes:

1. Medicinal products authorised in Malta through the National Procedures in line with Regulation 4(1) and 4(2) of the Medicines (Marketing Authorisation) Regulations[39]
2. Medicinal products authorised in Malta through the European Mutual Recognition Procedure (MRP)[4]
3. Medicinal products authorised in Malta through the European Decentralised Procedure (DCP).[4]

The following data was captured from the Malta Medicines List: 1) Medicine name, 2) Product reference number, 3) Active ingredient, 4) Therapeutic class, 5) ATC code, and 6) Authorisation date.

All medicinal products were subsequently analysed in order to associate an ATC code. Second level ATC codes were used to assess the therapeutic coverage.

[4] European Commission. Volume 2B Notice to Applicants Medicinal products for Human Use – Presentation and Format of the Dossier - Common Technical Document [Online]. Brussels: EC; 2008b [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

[38] Malta Medicines Authority (MMA). Malta Medicines List [Online]. Malta: MMA; 2015 [cited 2016 June 15]. Available from: URL: http://www.medicinesauthority.gov.mt/home?l=1

[39] Ministry for Justice. Subsidiary Legislation 458.34, Laws of Malta. Legal Notice 324 of 2007. Medicines (Marketing Authorisation) Regulations. Government Gazette: Malta; 2007.

2.4.1.3 Medicinal products available through the Maltese National Health Service

The GFL published on the Ministry for Health website was used as the data source. The GFL includes all medicinal products available through the Maltese NHS provided to patients for free. The following data was captured from the GFL: 1) Non-proprietary name of the medicinal products, 2) Dosage form, 3) Dosage strength, 4) Disease category, and 5) ATC code.

All medicinal products were subsequently analysed in order to associate an ATC code. Second level ATC codes were used to assess the therapeutic coverage.

2.4.1.4 Statistical data of gap analysis

Second level ATC codes obtained from the: 1) List of centrally authorised medicinal products, 2) List of authorised medicinal products in Malta, and 3) List of medicinal products present of the Maltese GFL, were imported in Microsoft Access® 2010. Structured Query Language (SQL) queries and analysis was run on the data set to show the spread of products and to identify any therapeutic gaps. A query was designed to highlight unmatched records comparing the therapeutic subgroup coverage of the CAP list, Malta Medicines List, GFL to the complete ATC classification list at the second level.

The percentage impact of lack of treatment alternatives in Malta if CAPs are not available was calculated with Microsoft Excel® 2007 using the following data:

1. Full list of second level ATC codes
2. ATC codes of medicinal products authorised in Malta and total number of medicinal products with corresponding ATC codes
3. ATC codes of CAPs and total number of medicinal products with corresponding ATC codes
4. Number of ATC codes of CAPs not available in Malta.

In the context of the gap analysis, a percentage impact of more than 10% was assumed to have impact on public health in Malta.

2.4.1.5 Outcomes of gap analysis

To understand the Maltese scenario with regards to accessibility of CAPs including innovative medicines, interviews were coordinated with the:

1. MMA to identify challenges from a regulatory perspective
2. DPA to identify challenges from the perspective of the entity responsible for health technology assessment and the formulary system
3. Central Procurement and Supplies Unit (CPSU) to identify challenges from the entity responsible of the procurement and supply of medicines for the government hospitals and clinics and for the patients who are entitled to free medicines.

The interviews were based on open-ended questions, where discussion could take place with the interviewee. The objectives of the interviews were to obtain information on:

1. Challenges which have been overcome and other challenges being encountered in line with innovative medicines
2. Initiatives which have been taken and are being taken by MMA, DPA and CPSU through the years to optimise access to medicinal products in Malta
3. Future plans to ensure that the NHS in Malta remains sustainable whilst ensuring that Maltese patients have access to medicinal products, including innovative medicines.

2.4.2 Use of existing legislative tools to improve access of centrally authorised products in Malta

Effective use of legislative tools to improve access of CAPs in Malta over 2015-2016 was analysed. The number of CAPs imported in Malta by the Maltese NHS between 2015-2016, using the following legislative tools was sourced from the Ministry for Health:

1. Approval by the Licensing Authority for a product to be allowed in exceptional cases, subject to such conditions as the Licensing Authority may attach to it as outlined in Article 20 (1) of the Medicines Act, 2003[40]

[40] Ministry for Justice, Culture and Local Government. Chapter 458 Medicines Act [Online]. Malta: The Ministry; 2003: 1-52 [cited 2017 May 05]. Available from: URL: http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1

2. Use of an unlicensed medicinal product on a named patient basis, for a specific patient (applies to both the Government Health Services and the private sector); by a Hospital Department within the Government Health Services; or by a Hospital / Clinic in the private practice[41]
3. Parallel distribution in accordance with Article 57(1)(o) of Regulation (EC) No 726/2004.[3]

[3] European Commission. Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [Online]. Official Journal of the European Union 2014; L136:1-33 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF

[41] Ministry for Health. Unlicensed medicinal products [Online]. Malta: Ministry for Health; 2017 [cited 2017 May 05]. Available from: URL: https://health.gov.mt/en/Pharmaceutical-Unit/Pages/Unlicenced-Medicinal-Products.aspx

CHAPTER 3

RESULTS

The results chapter includes the:

1. Review of European regulations on the authorisation processes of innovative medicines;
2. Available early access tools identified to facilitate timely access of innovative medicines to patients in Europe;
3. Glossary of regulatory terms to be used in a pharmaceutical and academic setting;
4. Use of conditional and exceptional authorisations as early access tools and the clinical studies presented during evaluation to obtain a positive outcome during evaluation of medicinal products authorised under conditional and exceptional circumstances;
5. Innovative medicines products available in Malta through the Maltese NHS and use of existing legislative tools to increase accessibility of innovative medicines in Malta.

3.1 Authorisation of innovative medicines

The processes by which innovative medicines are authorised were identified from the following directives and regulations:

1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.[2]

[2] European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2001; L311:67-128 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=EN

2. 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.[42]
3. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.[3]
4. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.[7]
5. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.[9]

[3] European Commission. Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [Online]. Official Journal of the European Union 2014; L136:1-33 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF

[7] European Commission. Regulation No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products [Online]. Official Journal of The European Union 2000; L18:1-5 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

[9] European Commission. Regulation No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006 [Online]. Official Journal of The European Union 2006; L378:20-21 [cited 2017 May 05]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf

[42] European Commission (EC). Directive 2001/84/EC of the European Parliament and of the Council of 27 September 2001 on the resale right for the benefit of the author of an original work of art [Online]. Official Journal of the European Union 2001; L272:32-36 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0084:EN:HTML

6. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.[10]
7. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.[43]
8. Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority".[44]
9. Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.[45]

[10] European Commission. Regulation No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products [Online]. Official Journal of The European Union 2007; L324:121-137 [cited 2017 May 05]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394_cons_2012-07/reg_2007_1394_cons_2012-07_en.pdf

[43] European Commission (EC). Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [Online]. Official Journal of the European Union 2014; L158:1-76 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014:158:FULL&from=EN

[44] European Commission (EC). Regulation No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority" [Online]. Official Journal of the European Union 2000; L103:5-8 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf

[45] European Commission (EC). Regulation No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council [Online]. Official Journal of the European Union 2006; L92:6-9 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf

10. Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required.[46]

EMA has launched several initiatives since 1995 to facilitate access of innovative medicines to patients. EMA initiatives have led to the introduction of the following early access tools: 1) Accelerated assessment, 2) Adaptive pathways, 3) Compassionate use, 4) Conditional marketing authorisation, 5) Marketing Authorisation under exceptional circumstances, 6) PRIME (Priority Medicines) Scheme, and 7) Scientific advice and protocol assistance.

3.2 Glossary of regulatory terms

A total of 270 terms related to the pharmaceutical regulatory field were defined. The terms together with a definition were listed in alphabetical order and divided into sections according to the first letter of the term. The terms range from 'Abuse' to 'World Health Organisation'. The author and date was included after the definition of the term. A 'References' section was included at the end of the glossary. Following pilot validation, suggested changes to the glossary were made and more terms were included and defined.

[46] European Commission (EC). Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required [Online]. Official Journal of the European Union 2014; L107:1-4 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_357/reg_2014_357_en.pdf

The following 10 terms were added following pilot validation: 1) Chemistry, Manufacturing and Control (CMC), 2) Efficacy, 3) Electronic Common Technical Document (eCTD), 4) eSubmission Gateway, 5) European Pharmacovigilance Issues Tracking Tool (EPITT), 6) Eudravigilance website (EVWEB), 7) Good Practice (GxP), 8) Quality, 9) Safety, and 10) Significant benefit.

After all the terms were defined, the glossary was finalised and presented in a 74-page A5 size booklet (Appendix 1).

3.3 Review of early access tools

The European pharmaceutical legislation has evolved to support the medicine development process from an early stage and to offer regulatory mechanisms to help promising new medicines reach patients as early as possible. Several regulatory tools and initiatives are being developed to foster patient early access to new medicines that address public health needs and are eligible for the centralised procedure.

3.3.1 Accelerated assessment

Regulation (EC) 726/2004[3] states that "in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining

[3] European Commission. Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [Online]. Official Journal of the European Union 2014; L136:1-33 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF

temporary authorisations subject to certain annually reviewable conditions". The criteria for requesting submission for accelerated assessment are:

- Justification that the medicinal product is of major public health interest
- Demonstration of therapeutic innovation
- Submission of a Letter of Intent by prior notification (allow around 70 days or more prior to the marketing authorisation application)
- Request for accelerated assessment prior to submission of marketing authorisation application (at least ten working days)
    - Demonstration that medicinal product is the first available treatment and/or has an advantage over an existing treatment by showing superior effectiveness with evidence of improved efficacy via direct comparative clinical trial results, evidence of improved safety (no important reduction to benefit). There has to be major contribution to patient care, such as new model/route of administration, treatment alternative, and different response from other treatments
    - Avoid serious side-effects of previously available treatments
    - Improve diagnostic capabilities (early diagnosis most often leads to improved outcomes).

The CHMP conducts an accelerated assessment in a maximum of 150 days. If major objections are identified during the assessment, the CHMP can revert to the normal timetable for the centralised procedure, which allows a maximum of 210 days (Article 6 (3) of EC Regulation 726/2004).

In December 2014, a group composed of members of the CHMP and EMA representatives was established to explore ways, within the current regulatory framework, to further support the development of new medicines addressing major public health needs. As a result, a scheme was developed to reinforce early dialogue and regulatory support to stimulate innovation, optimise development and enable accelerated assessment of PRIority Medicines, referred to as PRIME.

In March 2016, EMA launched the PRIME scheme to enhance support for the development of medicines that target these unmet medical needs. Through the scheme, the Agency encourages developers to focus on medicines likely to make a difference to patients. PRIME is designed to promote accelerated assessment and will also help medicine developers to make the best use of EMA's other early access routes. The scheme facilitates early dialogue between the various stakeholders, which is crucial to optimise the use of these tools.

With PRIME, applicants for marketing authorisation get additional advice and support if their products are expected to be eligible for accelerated assessment and fall within the scope of the centralised procedure. It also builds on other existing regulatory tools in place within the EU legal framework, including scientific advice and protocol assistance.

3.3.2 Compassionate use

Compassionate use is a tool used for the early access of promising medicines which have not yet been authorised (licensed) for the indicated conditions to patients with an unmet medical need. In the EU, a medicine can only be launched on the market after authorisation. In certain circumstances, access to medicines before authorisation is required for the benefit of the patients. Special programmes can be set up to make these medicines available to them under defined conditions, known as 'compassionate use'.[47]

Compassionate use programmes can be used in cases where medicines are expected to help patients with life-threatening, long-term or seriously debilitating diseases. Seriously ill patients are anticipated to benefit from compassionate use programmes since no alternative satisfactorily treatment with authorised medicines is available, or no treatment indicated for the disease has yet been authorised. Compassionate use progamme may be an effective early access tool for patients who are not eligible and cannot enrol in an ongoing clinical trial to acquire treatment with a potentially life-saving medicine. Knowledge of the medicine's safety may be limited during clinical trials. Toxicology studies would have been completed and analysed. At this stage of medicine development, there may still be some uncertainties on how the medicine can be made accessible to patients, such as the exact dose, posology, and the medicine's safety profile.

[47] European Medicines Agency (EMA). Questions and answers on the compassionate use of medicines in the European Union [Online]. UK: EMA; 2010 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500069898.pdf

The CHMP can provide recommendations to all EU member states on how to control, distribute and use medicines for compassionate use.[47] The CHMP identifies patients for whom compassionate use programmes may be beneficial, and provides recommendations following a request from a member state. The recommendations are intended to be used together, and do not replace, national legislation. The CHMP do not create any legal framework in the EU member states. The recommendations are not compulsory, and are only implemented by member states that wish to use them for their patients with the aim to standardise compassionate use programmes across the EU. The committee has also a role in assisting to make the conditions of existing compassionate use programmes more clear.

3.3.3 Conditional marketing authorisation and authorisation under exceptional circumstances

In 1993, the EU introduced an instrument to authorise medicines under exceptional circumstances. Early market access could be granted if an applicant was unable to obtain comprehensive data on safety and efficacy for ethical reasons or due to the rarity of the disease involved.[2] The sponsors, however, were committed to perform further studies to meet "specific obligations" after obtaining marketing approval. Under this regulation, many orphan drugs were initially approved; however, this regulatory pathway was expanded to include medicines intended for more common indications with a perceived high unmet medical need, such as acquired immune deficiency syndrome (AIDS).

[2] European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2001; L311:67-128 [cited 2017 May 05]. Available from: URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=EN

3.3.3.1 Conditional Marketing Authorisations

In the early 2000s, the EC wanted to clarify the difference between faster drug approvals for which additional data were required and approvals for which additional data were not expected (Breckenridge and Walley, 2008). The EC therefore replaced the original exceptional circumstances instrument with two regulatory pathways.

1. Approval under exceptional circumstances, which is similar to the original premise of the old exceptional circumstances pathway, is used for drugs for which the applicant is unable to provide the EMA/CHMP with comprehensive data on efficacy and safety.
2. CMAs of medicines are used for authorisations based on less comprehensive data but with demonstrated positive benefit–risk balance and expectation of more data in the near future.[45]

For both types of authorisations, the same post-marketing commitments apply as for standard applications. The new exceptional circumstances pathway attempts to avoid the situation in which medicines have permanent CMA status.

Medicines can be authorised under the CMA pathway only if they are intended to fulfil unmet medical needs, that is, are meant for diseases for which no treatment is currently available or if they confer a major therapeutic advantage. The intended use of CMA is for (i) seriously debilitating or life-threatening diseases, such as AIDS, (ii) emergency situations, and (iii) medicines designated as orphan medicines. CMA is intended to

[45] European Commission (EC). Regulation No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council [Online]. Official Journal of the European Union 2006; L92:6-9 [cited 2017 May 05]. Available from: URL: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf

enable early access of promising medicinal products to the public by abridging the development phase (Eichler et al, 2008). Speeding up the review process is not a key objective of CMA or authorisation under exceptional circumstances (Reichert and Healy, 2001), however a longer review process would contradict the purpose of accelerating access to these medicines. Some authors have raised doubts about the quality of this type of approval, especially regarding safety, frequent use of surrogate end points, and difficulties in enforcing compliance with post-authorisation commitments.[48]

For CMAs, the sponsor is committed to fulfil post-marketing obligations, including conduct of new studies to help substantiate a positive benefit–risk ratio, collecting pharmacovigilance data and periodic safety update reports (PSURs), to obtain a definitive authorisation, based on full safety research and testing, or the product may be withdrawn from the market. It is recommended that the product sponsor should notify the EMA of its intentions to request a CMA as part of its Letter of Intent.

For the CMA to be effectively implemented, a level of transparency is required for the post-marketing obligations. The list of obligations for a CMA must be made publicly accessible, as well as the timeline for meeting each obligation. The labelling and patient information should also reflect the "conditional nature" of the marketing authorisation, which may include the "black triangle" to ensure healthcare professionals are aware that an advanced monitoring system is required for such medicinal products. Financial penalties are imposed in cases of infringement of the specific obligations.

[48] US Government Accountability Office. New drug approval - FDA needs to enhance its oversight of drugs approved on the basis of surrogate endpoints [Online]. Washington: FDA; 2009 [cited 2017 May 05]. Available from: URL: http://www.gao.gov/assets/300/295762.pdf

The CMA is valid for one year and can be renewed provided the MAH applies for renewal of the marketing authorisation before its expiry. During this renewal process, the benefit-risk ratio is reassessed to ensure it remains positive. The status of the specific obligations and the set timeframes for meeting these obligations are reviewed. On fulfilment of all specific obligations, the CMA may convert to a "normal" marketing authorisation.

3.3.3.2 Marketing authorisation under exceptional circumstances

Medicinal products can be granted a marketing authorisation under exceptional circumstances when the applicant can demonstrate in this application that comprehensive data on the efficacy and safety under normal conditions of use cannot be provided due to:

- Indications for which the medicinal product is indicated are very rare that the applicant cannot practically be expected to provide comprehensive data
- In the present circumstances of scientific knowledge, comprehensive evidence cannot be provided
- It would be contrary to generally accepted principles of medical ethics to collect such information (may be eligible for marketing authorisation under exceptional circumstances).[49]

[49] European Medicines Agency (EMA). European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure [Online]. UK: EMA; 2017 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf

Marketing authorisation under exceptional circumstances is granted conditional on a requirement for the applicant to introduce specific measures, particularly with regards to the safety of the medicinal product, notification to the competent authorities of any adverse event in relation to its use, and follow-up measures to be taken. An authorisation under exceptional circumstance would not be granted if the CHMP deems that a conditional marketing authorisation is more apt.

Unlike the CMA, where marketing authorisation is granted in the absence of comprehensive data in the likelihood that the sponsor is poised to provide such data within an agreed timeframe, approval under exceptional circumstances circumvents the inadequacy of the product sponsor to provide comprehensive data by setting obligations intended for the provision of safety and efficacy data on the medicine's intended use. It may be unlikely that a full dossier can be submitted. However, on rare occasions, where a full dossier becomes available and no specific obligations remain, a normal marketing authorisation could be granted.

The product sponsor is advised to put forward a proposal for a programme of study particularly with regards to the safety of the medicinal product, including detailed pharmacovigilance activities, RMP, prescription or conditions of use, and transparency in the product information. The packaging leaflet must show that the information available for the concerned medicinal product is incomplete in specified areas.

The marketing authorisation under exceptional circumstances is valid for five years on a renewable basis, however is subject to annual re-assessment of the benefit–risk ratio by the CHMP. The CHMP reviews the information provided during the assessment phase

and will determine authorisation if there are sufficient grounds for the approval of the medicinal product under exceptional circumstances. The CHMP reviews the proposed "specific procedures" to address not only the impact of the proposed risk minimisation activities on the benefit–risk ratio and to determine if further studies can better inform on aspects that are important to the safe and effective use of the medicinal product.

Table 3.1 addresses the differences between the CMA and authorisation under exceptional circumstances and applicable scenarios of their use.

Table 3.1 Comparison between conditional marketing authorisation and authorisation under exceptional circumstances

Conditional marketing authorisation	**Authorisation under exceptional circumstances**
Granted before all data are available	Comprehensive data cannot be provided (e.g. too rare)
Authorisation valid for one year (renewable)	Annual reassessment of risk-benefit balance
Obligations: Further clinical studies to verify benefit/risk balance	Obligations: Specific procedures in particular concerning safety
Data package: *Initial + Obligations = Normal*	Data package: *Initial + Obligations < Normal*

3.3.4 Adaptive pathways

'Adaptive pathways' is a scientific model for medicine development and data generation allowing for timely and progressive patient access to medicines. The adaptive pathways concept uses existing EU regulatory framework for medicines.

The adaptive pathwaysconcept is based on three principles:

1. Iterative development, indicated a step-wise approval in stages, starting with a restricted patient population which then spreads out to wider patient populations; and confirming the benefit-risk balance of a medicinal product, following a conditional authorisationon the basis of early comprehensive information (using surrogate endpoints) considered predictive of significant clinical outcomes
2. Compiling evidence through real-life use in addition to and supportingclinical trial data
3. Early involvement of patients and HTA-bodies in discussions on a medicine's development.

The adaptive pathways scientific concept is directed to treatments in areas of high unmet medical need where it is difficult to collect data via established routes and where large clinical trials would needlessly expose patients who are unlikely to benefit from the medicine. The adaptive pathways model builds on regulatory processes already in place within the existing EU legal framework. These include:

- Scientific advice
- Compassionate use
- Conditional authorisation for medicines addressing life-threatening conditions
- Patient registries and other pharmacovigilance tools that permit the compilation of real-life data and development of the RMP for each medicine.

The adaptive pathways model does not revolutionize the standards for evaluation of benefits and risks or the requirement to display a positive benefit-risk balance to obtain marketing authorisation.

EMA ran a pilot project between March 2014 and August 2016 to investigate the practical implications of the adaptive pathways model with medicines which are still being development.[50] The pilot project provided a structure for informal dialogue between stakeholders, including patients and HTA-bodies, to consider different options in a setting considering detailed technical and scientific questions based on tangible examples. EMA received 62 applications and selected 18 proposals for face-to-face meetings. At the end of the pilot project, 6 applicants received parallel advice from EMA and HTA bodies and 1 applicant benefited from EMA's scientific advice.

In parallel to EMA's adaptive pathways project, the Innovative Medicines Initiative (IMI) runs ADAPT-SMART, a project examining the theoretical framework that could be used for the adaptive pathways approach, including tools and methodologies.[51] The adaptive pathways project, led by EMA, seeks to set up collaborative solutions to promote the development of Medicines Adaptive Pathways to Patients (MAPPs) in Europe, encouraging more efficient ways of developing and regulating medicines. Bringing together patients, regulators, industry, HTA-bodies, payers, and academics, ADAPT-SMART has the key objective to provide patients with more appropriate access to innovative medicines.

[50] European Medicines Agency (EMA). Workshop on adaptive pathways - discussing a concept for development of medicines addressing unmet medical needs [Online]. UK: EMA; 2016 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/09/news_detail_002595.jsp&mid=WC0b01ac058004d5c1

[51] Innovative Medicines Initiative (IMI). ADAPT-SMART, Accelerated development of appropriate patient therapies: a sustainable, multi-stakeholder approach from research to treatment-outcomes [Online]. Belgium: IMI; 2017 [cited 2017 May 05]. Available from: URL: https://www.imi.europa.eu/content/adapt-smart

3.3.5 Comparing early access tools

Understanding the difference between the existing, new, and emerging pathways, strategies, and approaches that have been or are being implemented by regulatory agencies and/or organisations is important (Table 3.2).

Table 3.2 Comparison of existing and new regulatory tools and pathways

Pathway/ Tool	Year of introduction	Status	Purpose	Assessment Basis	Mechanism for accelerated access
Approval under exceptional circumstances	1993	Existing	Medicines with urgent public health need	Non-comprehensive non-clinical and clinical data with little likelihood of being collected	Shortened development and authorisation time
Scientific Advice	2004	Existing	Advice to a company on appropriate tests and studies in development of a medicine	Not applicable	Support in medicines development and submission of application for authorisation
Compassionate Use	2004	Existing	Making a medicine available for compassionate reasons to patients with a chronically or seriously debilitating or life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product	Medicine must be the subject of an application for a marketing authorisation or medicine must be undergoing clinical trials. While early studies would generally have been completed, its safety profile and dosage guidelines may not be fully established	Shortened development time and earlier accessibility to patients
Conditional Marketing Authorisation	2005	Existing	Seriously debilitating and life-threatening conditions, medicine for emergency use, or orphan medicines; must address unmet medical need	Non-comprehensive data with little likelihood that there will be timely collection of additional data after authorisation.	Shortened development and authorisation time
Accelerated assessment	2005	Existing	Medicines of major interest to public health, particularly those expressing a therapeutic innovation	Requires justification by the sponsor of a major public health interest	Review time shortened to150 days as compared with the standard 210 days

Pathway/ Tool	Year of introduction	Status	Purpose	Assessment Basis	Mechanism for accelerated access
PRIME Scheme	2016	New	Medicines of major interest to public health, particularly those representing a therapeutic innovation	Early and proactive support to developers to optimise generation of robust data on a medicine's benefits/ risks and enable accelerated assessment of medicines	Support scheme for medicine development
Medicines adaptive pathways to patients (MAPP)	Not Applicable	Emerging	Medicines to treat an unmet medical need for a serious condition; to be applied more broadly with experience and strengthening post–initial authorisation systems for monitoring medicine utilisation and experience	Clinical safety, efficacy, relative effectiveness, and cost-effectiveness data, as appropriate, collected across the life cycle of the medicine and submitted for successive regulatory and reimbursement assessments and decisions	Shortened development cycle, and shortened regulator and payer/HTA review times

Adapted from: Baird LG, Banken R, Eichler HG, Kristensen FB, Lee DK, Lim JC, et al. Accelerated access to innovative medicines for patients in need. Clinical Pharmacology and Therapeutics 2014; 96(5):559-71.

3.4 Analysis of early access tools

The two early access tools used to bring innovative medicines, with incomplete comprehensive data at application submission, to the market were selected as the:

1. Conditional marketing authorisation (CMA)
2. Exceptional authorisation under exceptional circumstances

Early access tools are not mutually exclusive, for example a medicine benefitting from support under the PRIME scheme could also receive an opinion from CHMP on CMA while still undergoing clinical trials and can be granted a CMA before comprehensive data is available. Early access tools including accelereated assessment, compassionate use programmes and PRIME scheme can be used with conditional and exceptional authorisations during the same procedure.

Selection of conditional and exceptional marketing authorisation for in-depth analysis was confirmed with Professor John Joseph Borg, Post-Licensing Director at MMA and CHMP member for Malta.

3.4.1 Characteristics of conditional marketing authorisations and authorisations under exceptional circumstances

This study summarises the experience with CMAs since first use in 2006 to 2016, and with authorisation under exceptional circumstances from 2002 to 2016 as per data published by the EMA.

3.4.1.1 Number of registrations

From January 2006 to December 2016, 35 CMAs were granted, of which 11 were converted to “standard” marketing authorisations, 2 were withdrawn and the remaining 23 authorisations are still conditional. None of the marketing authorisation were revoked or suspended.

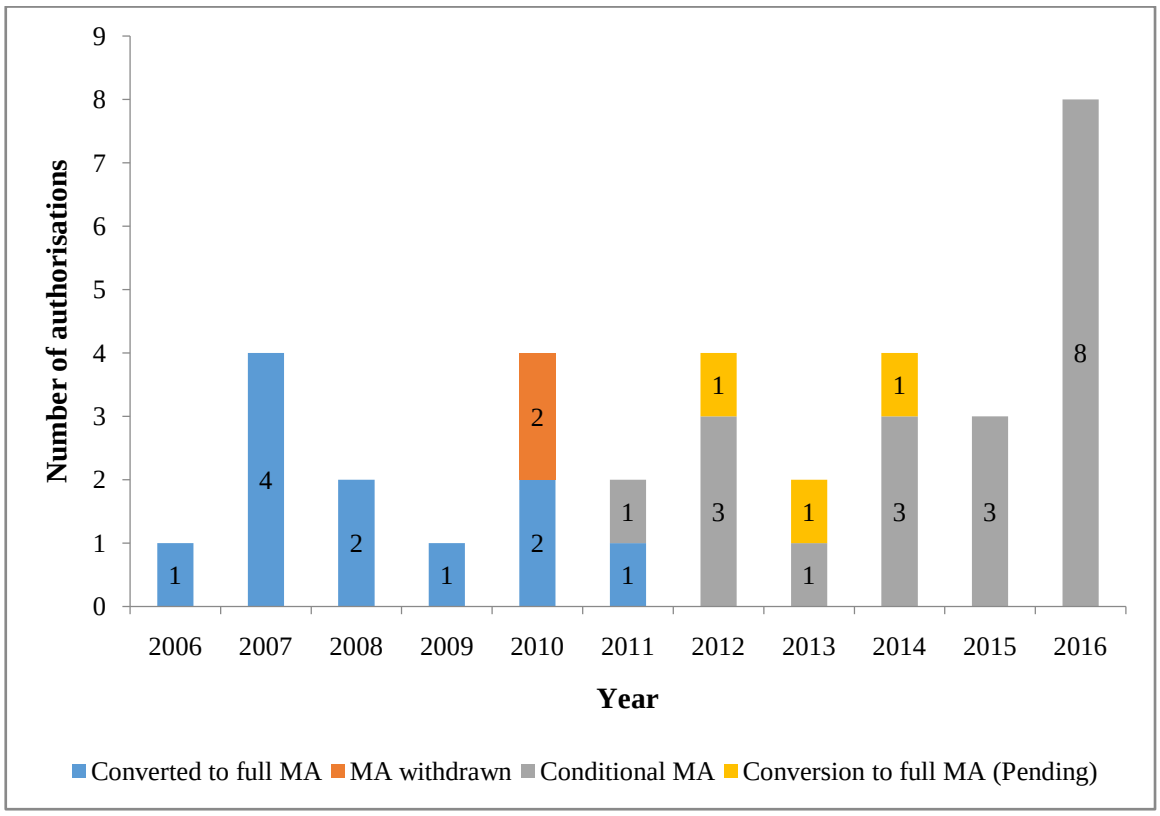

Figure 3.1 Number of conditional marketing authorisation granted from 2006-2016 (n=35)

For authorisations that are still conditional, none have been authorised for longer than five years. All authorisations granted up to 2011 were converted to ‘standard’ marketing authorisations. An increase in the number of CMAs was observed since the start of the conditional marketing authorisation in 2006 with a maximum of 4 authorisations per

year followed by a surge in 2016 with 8 authorisations (Figure 3.1). The two medicines which were withdrawn, Arepanrix® and Humenza® concerned pandemic influenza vaccines and both withdrawals were done for commercial reasons.

Thirty authorisations under exceptional circumstances were granted, of which 5 were withdrawn and the remaining 25 authorisations are still authorisations under exceptional circumstances. None of the marketing authorisations were revoked or suspended. A decrease in authorisations under exceptional circumstances was observed particularly since 2010. There were a peak number of 7 authorisations in 2009 (Figure 3.2).

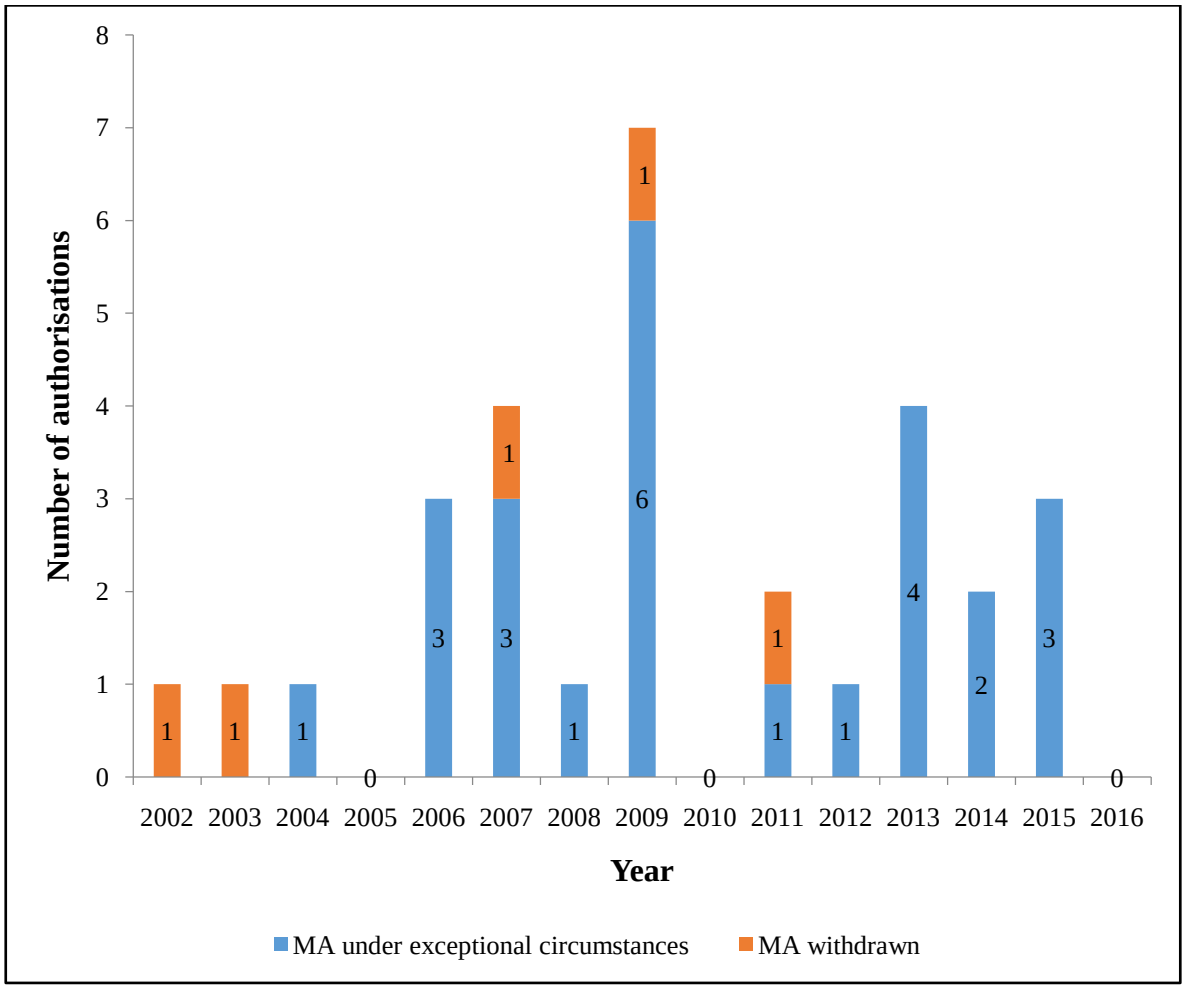

Figure 3.2 Number of authorisations under exceptional circumstances granted from 2002-2016 (n=30)

Pumarix® and Daronrix® indicated for pandemic influenza and Rilonacept Regeneron® (previously Arcalyst®) indicated for cryopyrin-associated periodic syndromes were never marketed in any of the member states and were withdrawn.

On the other hand, Pfizer Limited, the MAH of Onsenal®, conatining celecoxib and used for reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis, as an adjunct to surgery and further endoscopic surveillance, decided to voluntarily withdraw the marketing authorisation. The MAH was unable to provide the additional data required to fulfil its specific obligation, as a result of slow enrolment in an ongoing clinical trial. Onsenal® was marketed in all EU countries except for Bulgaria, Hungary, Malta, Romania and Slovenia.

The use of Xigris®, which contains the active substance drotrecogin alfa (activated), was restricted to the most severe sepsis patients (at least 2 organ failures) and had to be started within 48 hours, and preferably 24 hours, of the onset of severe sepsis. Eli Lilly's decided to withdraw Xigris® from the market worldwide and all ongoing clinical trials further to the 28-day mortality results from the PROWESS-SHOCK study.[52]

Results from the PROWESS-SHOCK studyfailed to meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients treated with Xigris® compared to placebo. The study also failed its secondary endpoint of a reduction in mortality in the population of patients with severe protein C deficiency.

[52] European Medicines Agency (EMA). Press release: Xigris (drotrecogin alfa (activated)) to be withdrawn due to lack of efficacy [Online]. UK: EMA; 2011 [cited 2017 May 05]. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/10/news_detail_001373.jsp&mid=WC0b01ac058004d5c1

Eighteenof the CMAs and 18 of the authorisations under exceptional authorisations were first considered during the procedure or re-examination (Figure 3.3). The distribution with regards to both types of marketing authorisations is similar. Normally, it would be expected to have a higher number of marketing authorisations under exceptional circumstances identified during the initial phases of marketing authorisation.

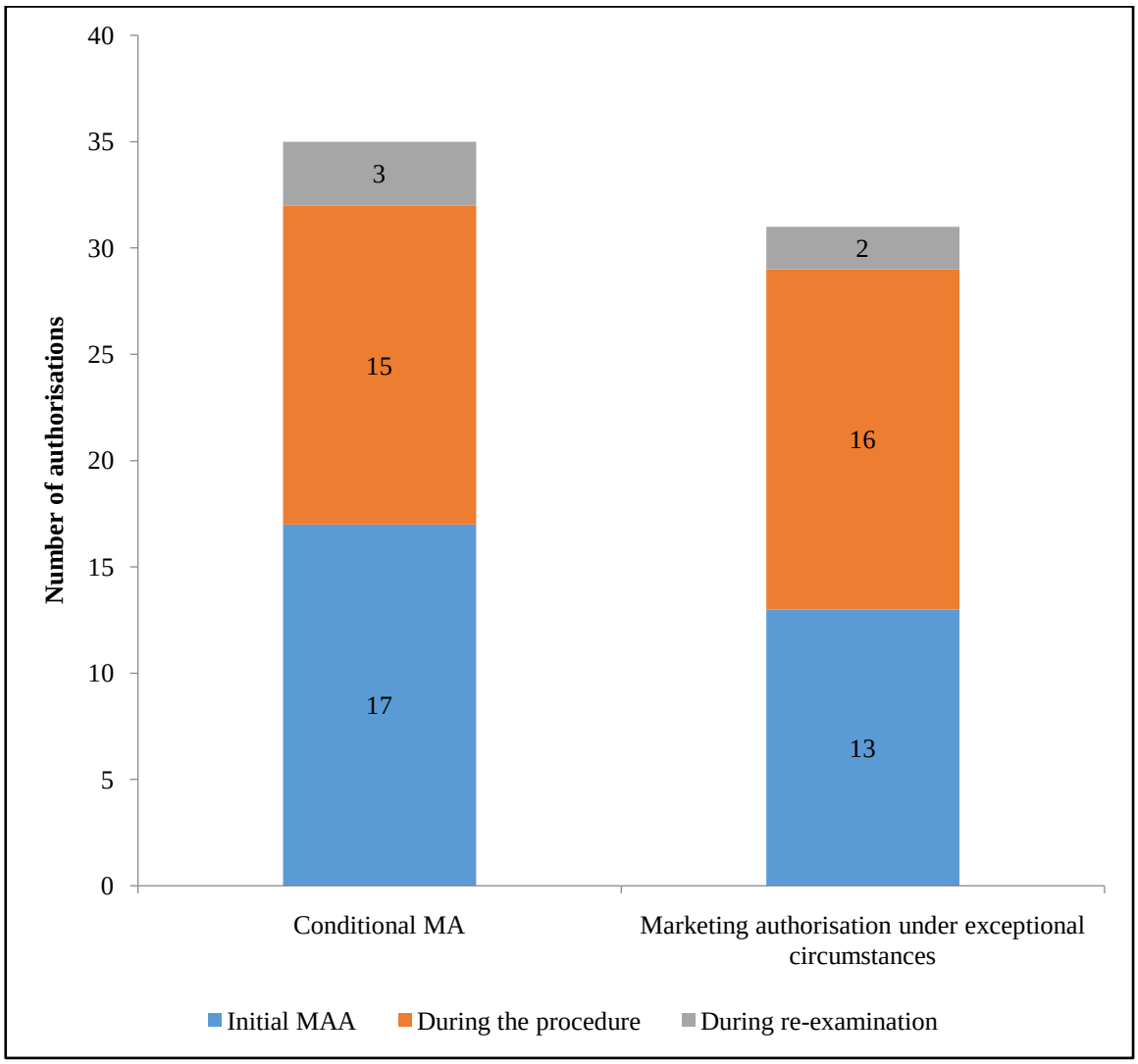

Figure 3.3 Stage of procedure when conditional or exceptional authorisation was first considered (n=65)

The time to marketing authorisation increases with the lateness in deciding the type of marketing authorisation, and is consistently greater at every stage of marketing authorisation (Figure 3.4). The average duration of the assessment of When CMAs and authorisations under exceptional circumstances were considered during initial applications, the average duration of the assessment was decreased by 89 days and 274 days respectively when compared with CMAs and authorisations under exceptional circumstances considered during re-examination.

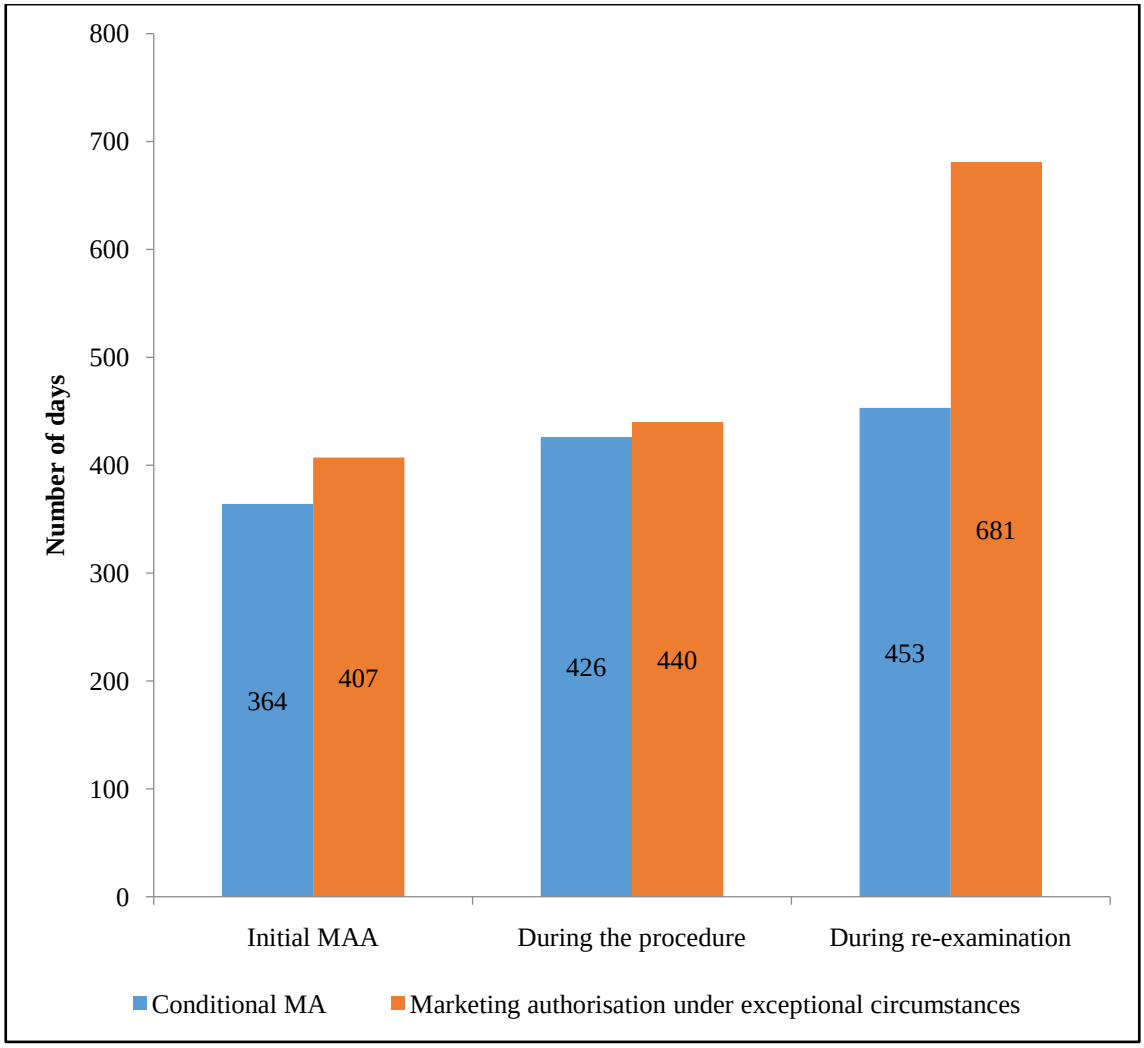

Figure 3.4 Average duration of assessment (including stop-clocks) by stage of first consideration of conditional marketing authorisation and authorisation under exceptional circumstances

3.4.1.2 Therapeutic Areas

Twenty-one of CMAs were in the oncology area, followed 9 CMAs for infectious diseases, and the remaining medicines for neurology or ophthalmology indications (Figure 3.5).

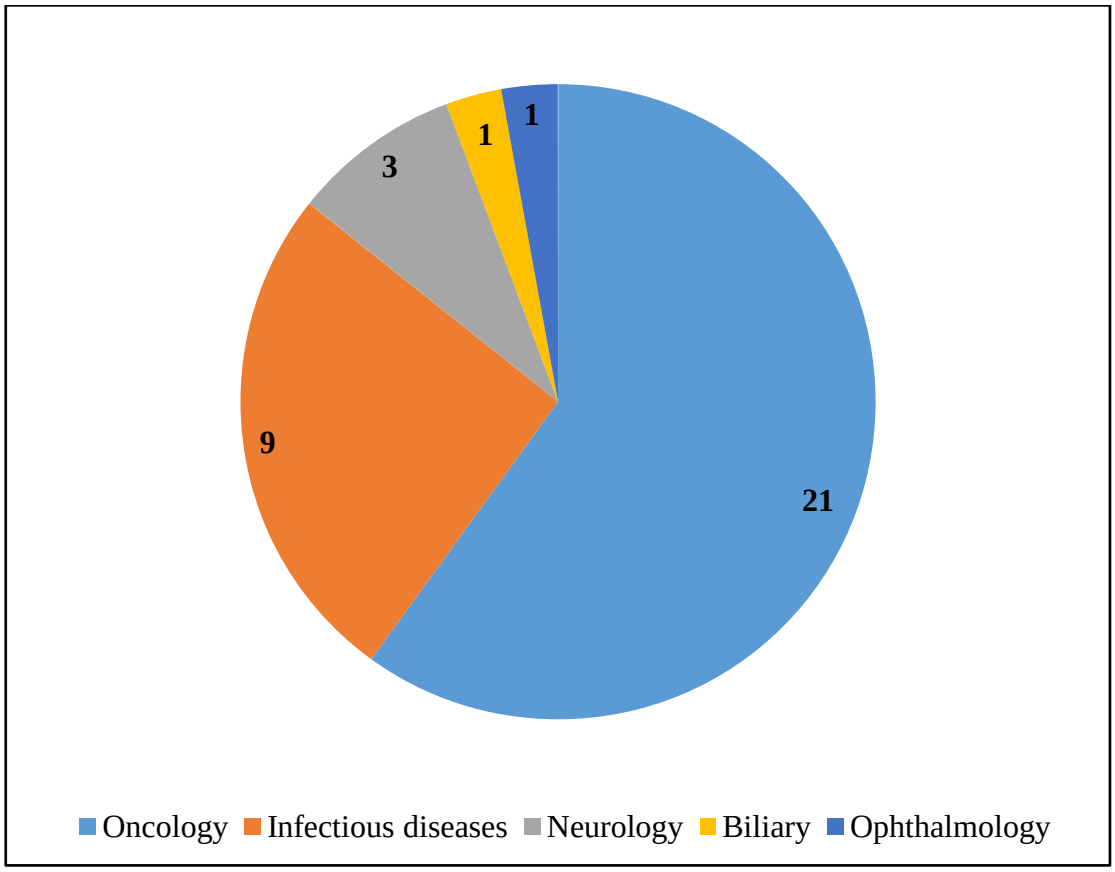

Figure 3.5 Therapeutic areas covered by conditional marketing authorisations (n=35)

Authorisations under exceptional circumstances cover a wider range of therapeutic areas including also cardiovascular diseases, dermatology, endocrinology and gastroenterology (Figure 3.6).

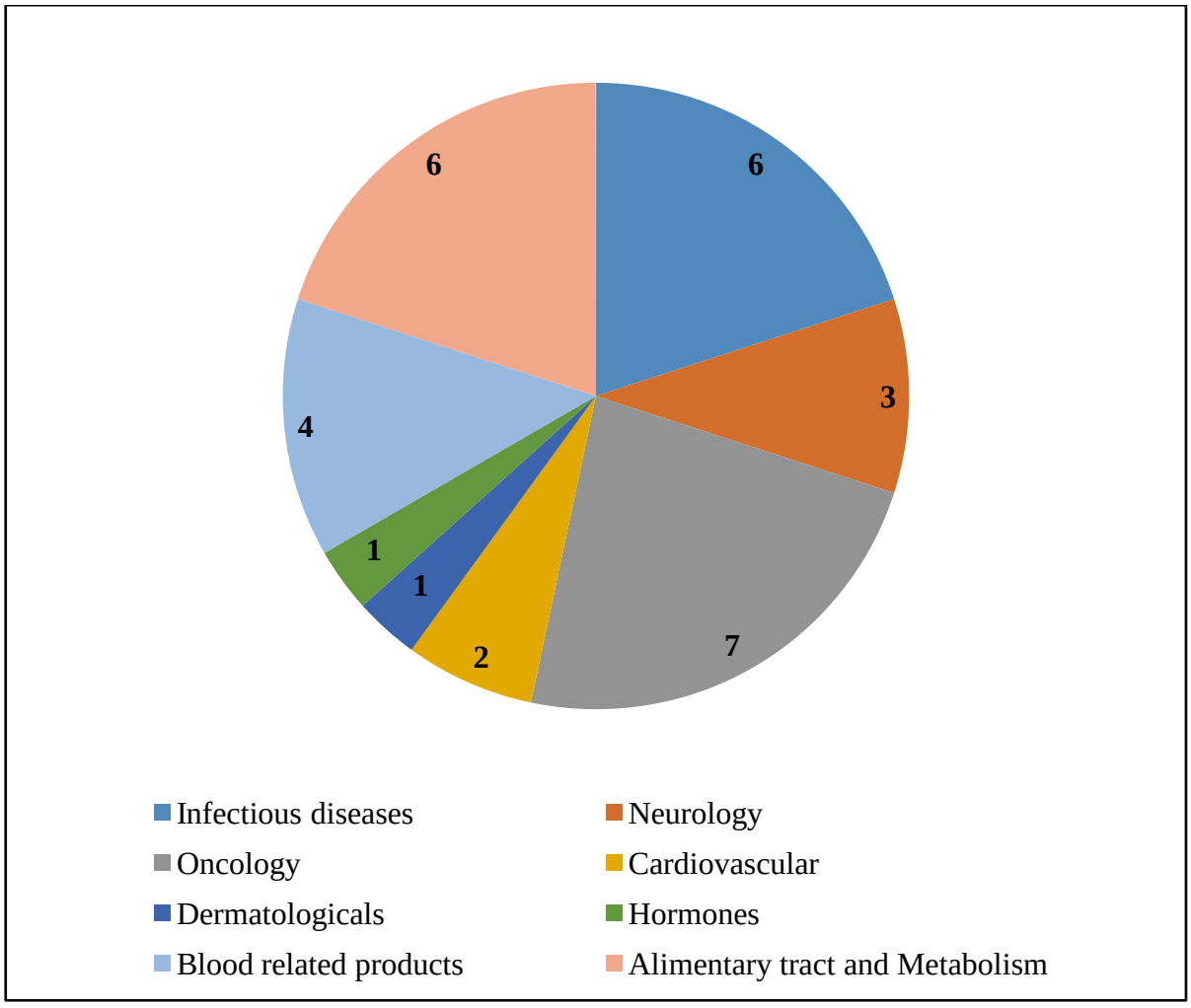

Figure 3.6 Therapeutic areas covered by authorisation under exceptional circumstances (n=30)

3.4.1.3 Orphan medicines

Since 2003, the conditional and exceptional regulatory pathways led to 33 authorised medicines designated as orphan medicines. Twenty out of 35 CMAs and 13 out of 30 authorisations under exceptional circumstances are orphan medicines (Figure 3.7). Two orphan medicines authorised under exceptional circumstances, Onsenal® and Rilonacept Regeneron® were withdrawn. There were one or more orphan medicines authorised in

the last 6 years wben compared to the previous 6 years. No orphan medicines were authorised in 2005 and 2010.

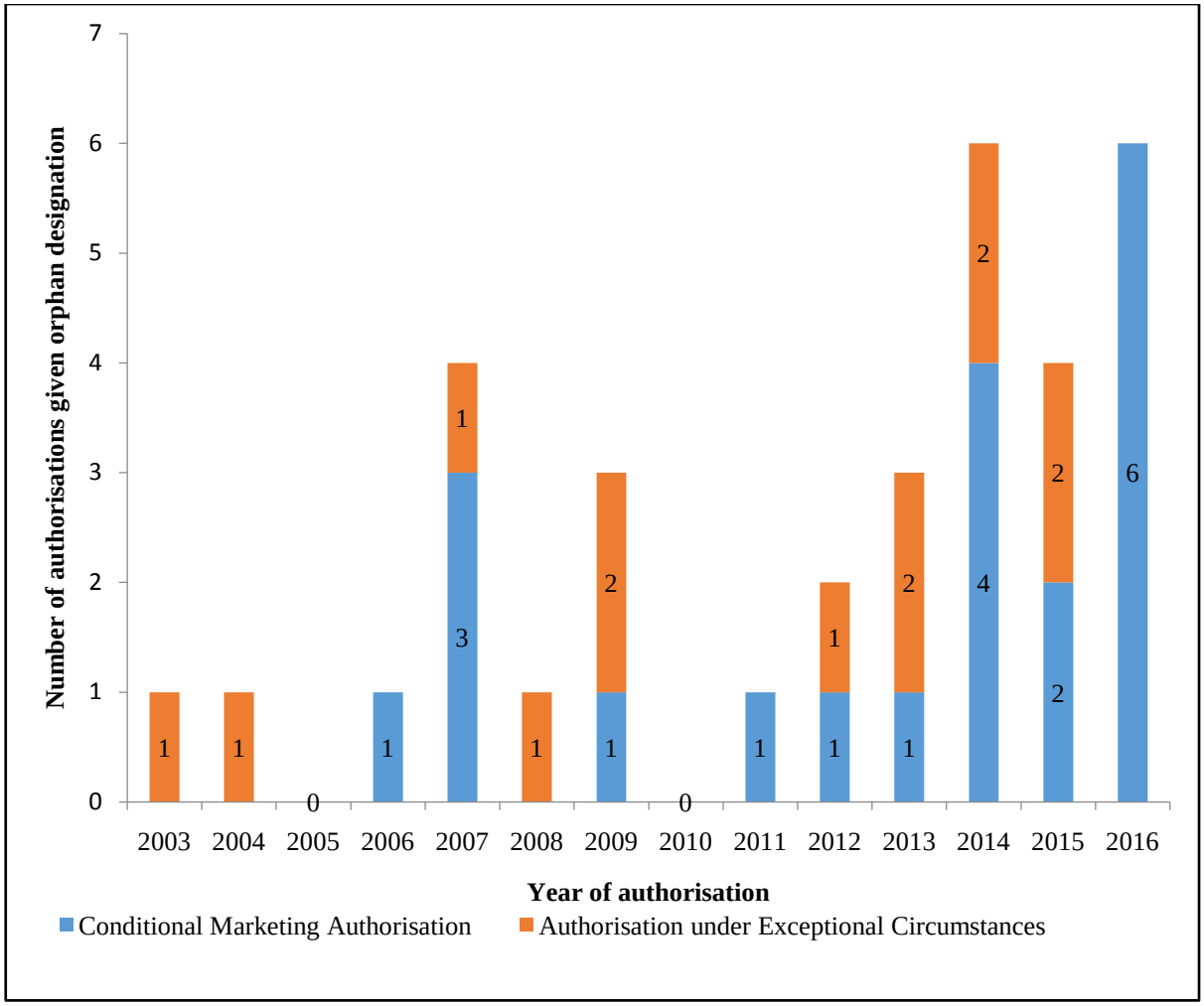

Figure 3.7 Authorised orphan medicines through conditional and exceptional authorisations per year (n=33)

3.4.1.4 New active substance status

The conditional and exceptional regulatory pathways have also led to 28 authorised medicines which were given a new active substance status since 2007. Fifty-seven per cent 20 out of 35 CMAs and 8 out of 30 authorisations under exceptional circumstances were new active substances (Figure 3.8). The number of new active substances was observed to increase since 2010 with a maximum of 7 new active substances in 2016.

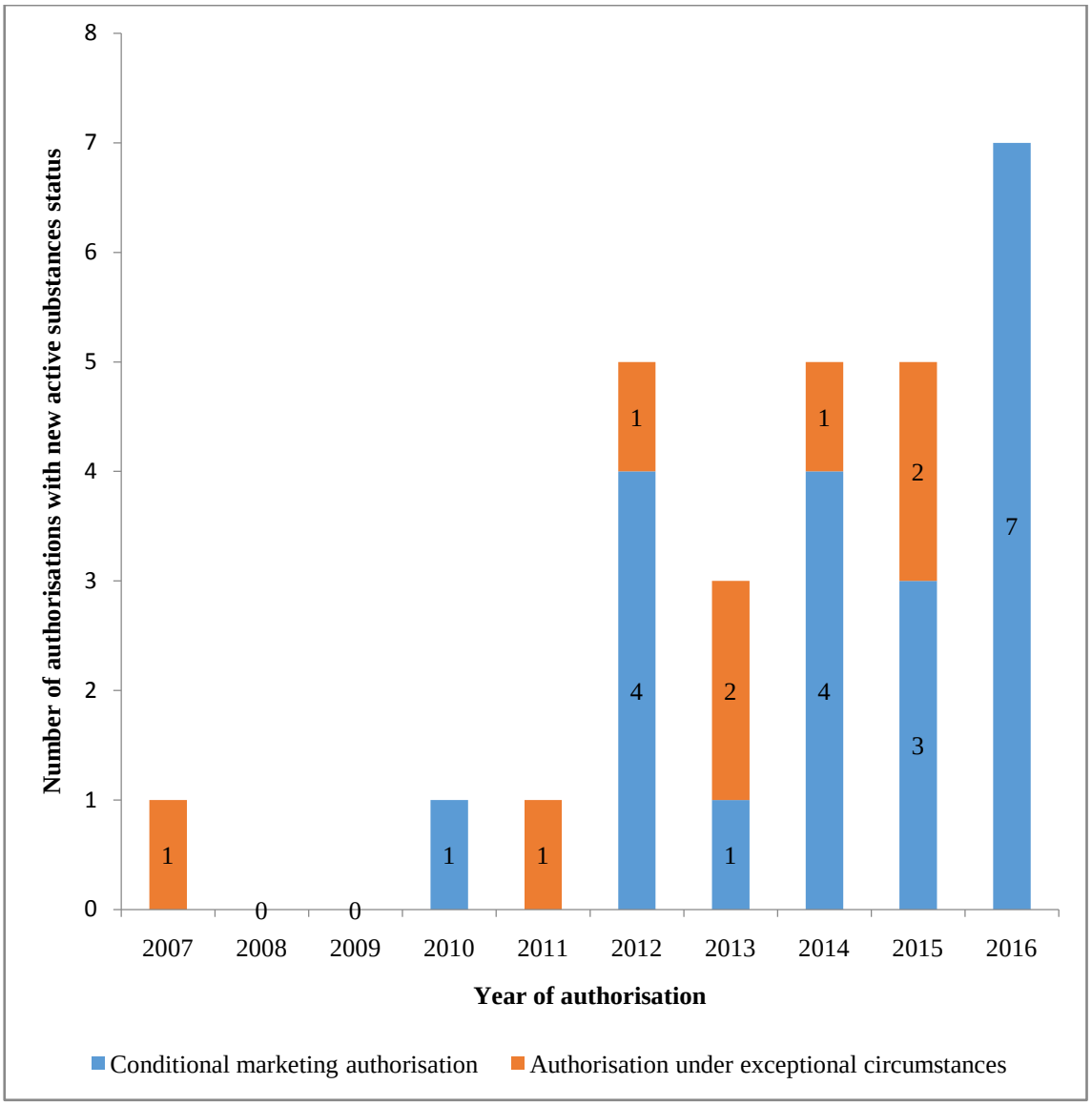

Figure 3.8 Authorised new active substances through conditional and exceptional authorisations per year (n=28)

3.4.1.5 Scientific advice and protocol assistance

Scientific advice or protocol assistance can be given by experts appointed by the EMA prior to submission of the initial application and during the application review process. MAHs of 22 CMAs used the tool of scientific advice or protocol assistance before or during the review process (Figure 3.9). Scientific advice or protocol assistance was used for 12 authorisations under exceptional circumstances (Figure 3.10).

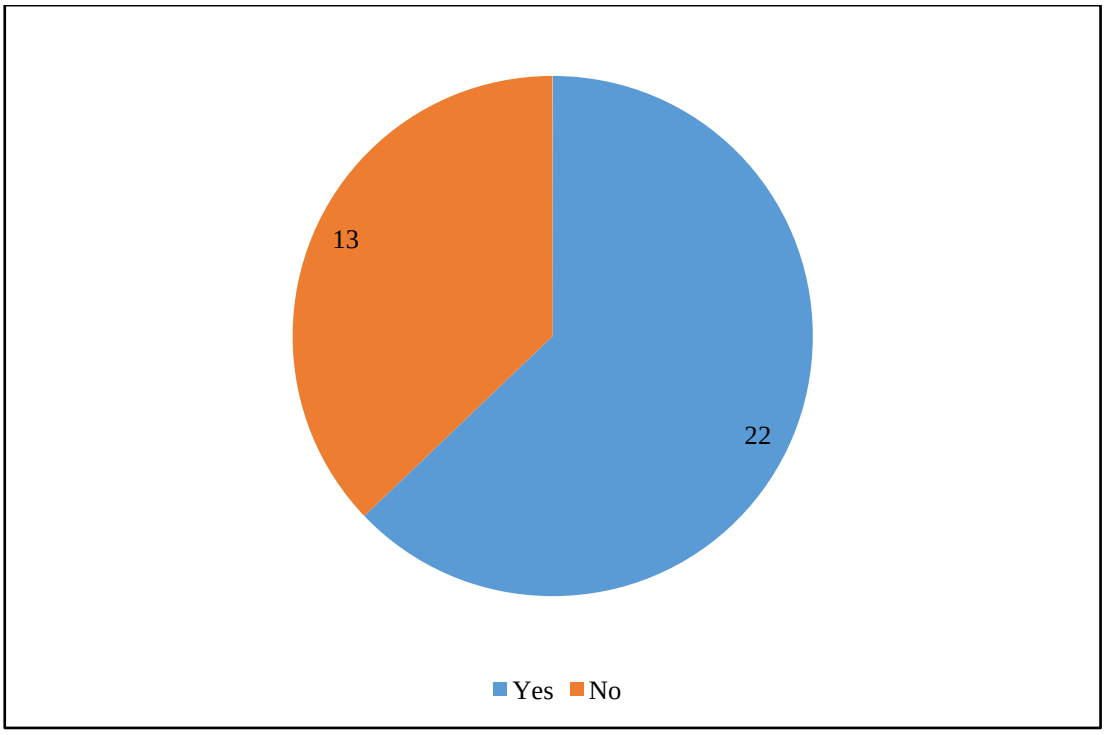

Figure 3.9 **Use of Scientific advice/protocol assistance in conditional marketing authorisations (n=35)**

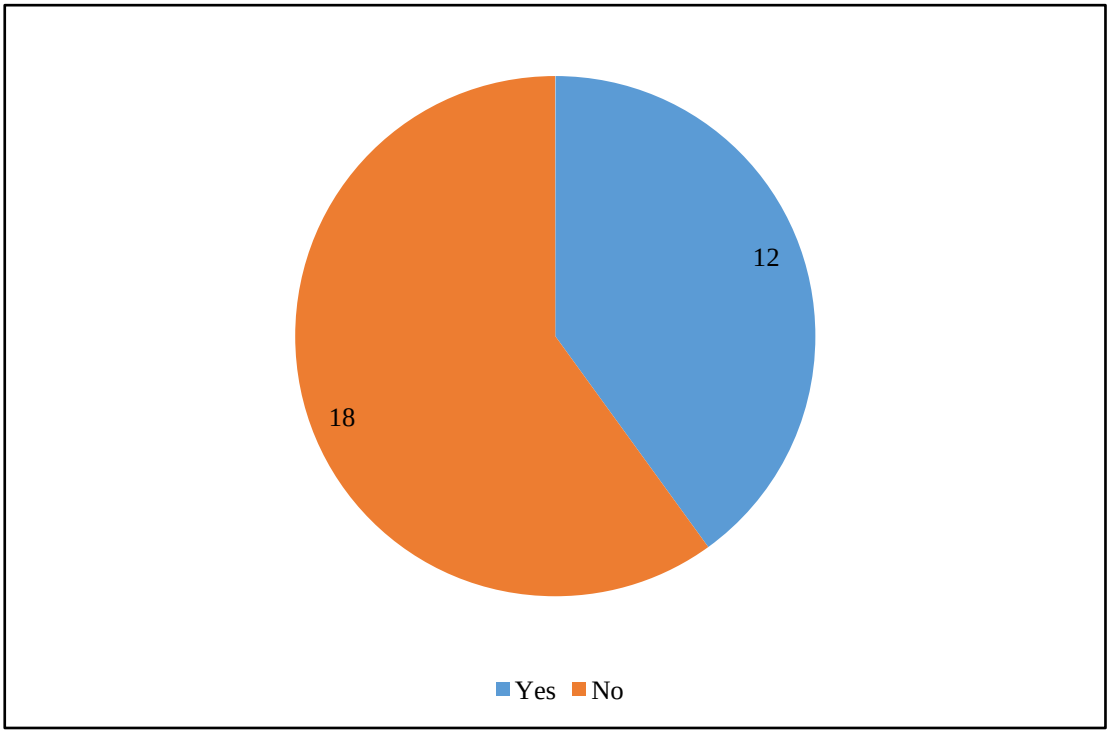

Figure 3.10 **Use of Scientific advice/protocol assistance in authorisations under exceptional circumstances (n=30)**

3.4.2 Data from European Public Assessment Report

The results of the pivotal studies are the main data used for discussion of the benefit-risk balance of the medicines under assessment, which leads to a positive or negative CHMP opinion for authorisation. Sixty-two pivotal studies were used for authorisation of the 35 CMAs.

3.4.2.1 Pivotal studies supporting conditional marketing authorisations

The studies used in conditionally authorised medicines were mostly phase II or phase III. Thirty-four out of 62 pivotal studies were phase II (including phase I/II and or IIb) and 23 studies were phase III (Figure 3.11). Out of the 35 CMAs, data from at least one complete phase III clinical trials was submitted for 16 authorisations.

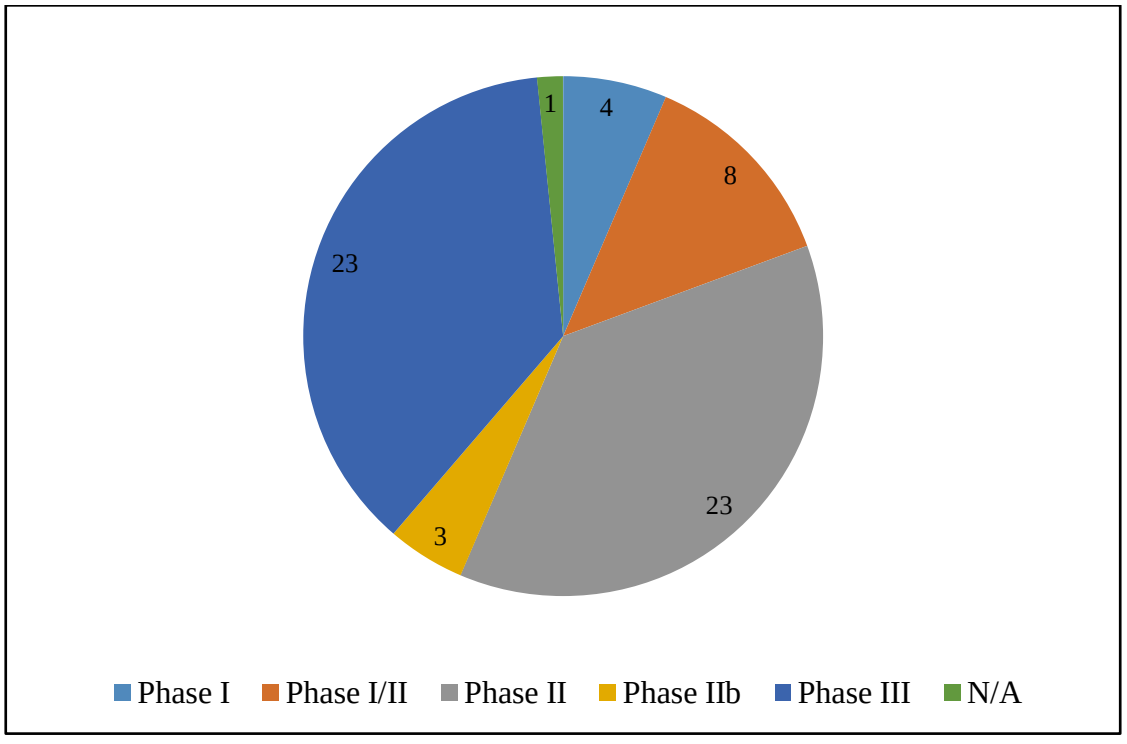

Figure 3.11 Studies identified as pivotal in assessment of the applications for conditional marketing authorisations according to phase (n=62)

In the largest therapeutic areas, infectious diseases and oncology, 8 and 10 of the clinical studies presented, respectively, were Phase III studies. Twelve of pivotal studies for products indicated in infectious diseases and 21 of the pivotal studies for oncology products were phase II studies (Figure 3.12).

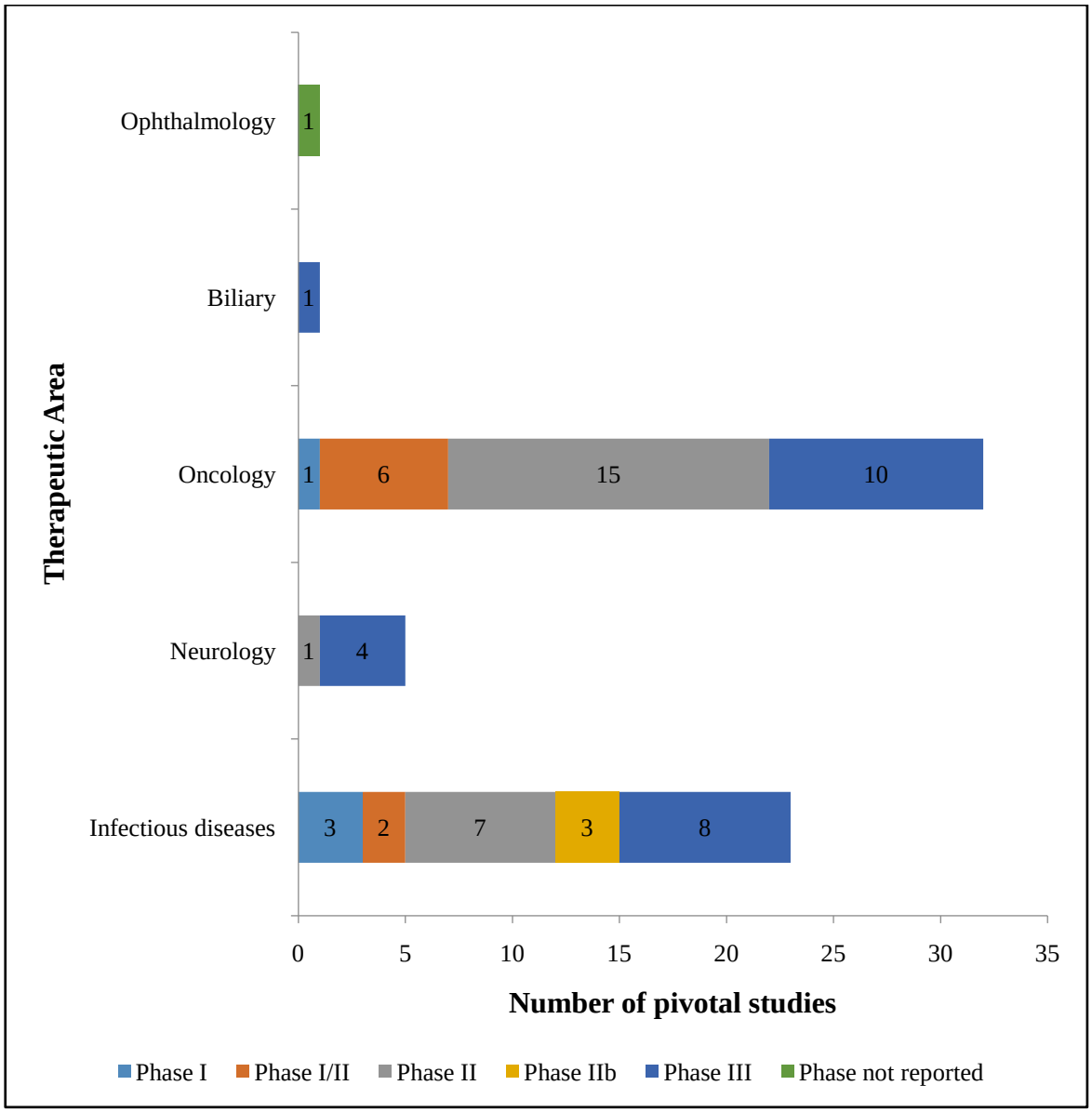

Figure 3.12 Distribution of pivotal studies by phase according to therapeutic area (n=62)

Thirty-four of the 62 pivotal studies were randomised multiple arm studies, followed by 22 (35%) non-randomised single arm studies (Figure 3.13).

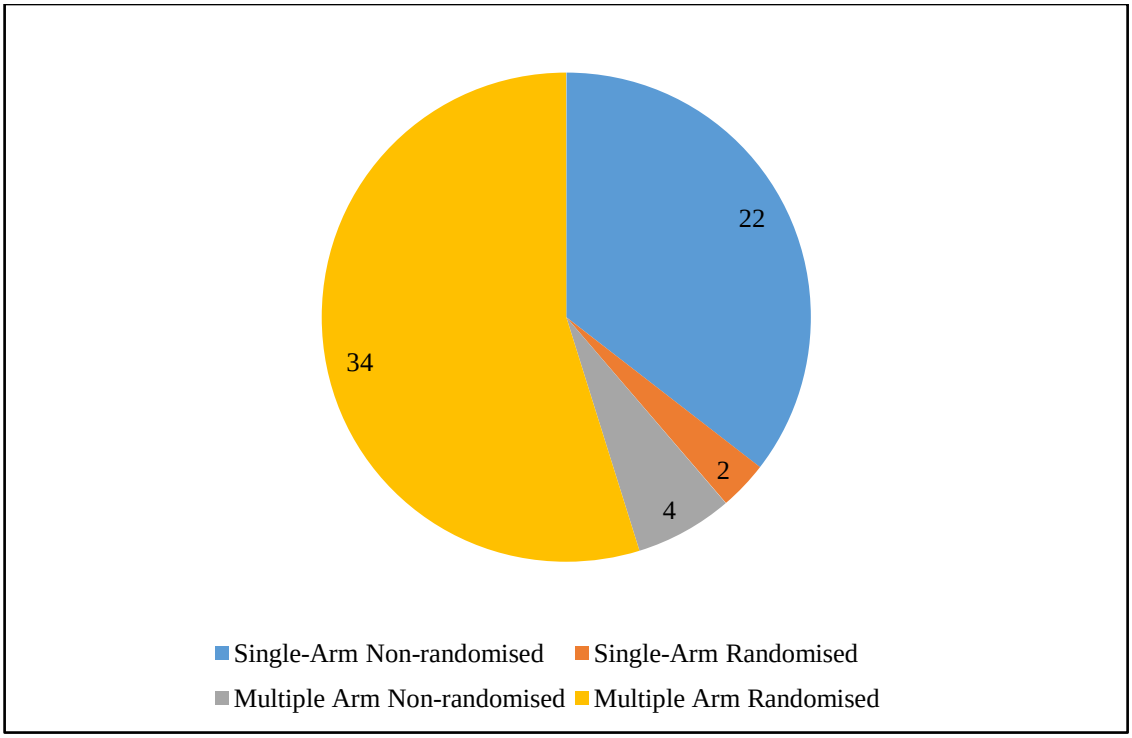

Figure 3.13 Pivotal study designs (n=62)

Nineteen out of 23 pivotal studies performed for products indicated for infectious diseases were multiple-arm studies. In the oncology therapeutic area, 13 multiple-arm studies out of 32 studies were performed. In the neurological and biliary therapeutic areas only multiple-arm studies were used. Single-arm studies were performed for 4 products for infectious diseases, 19 oncology products and 1 ophthalmology product (Figure 3.14).

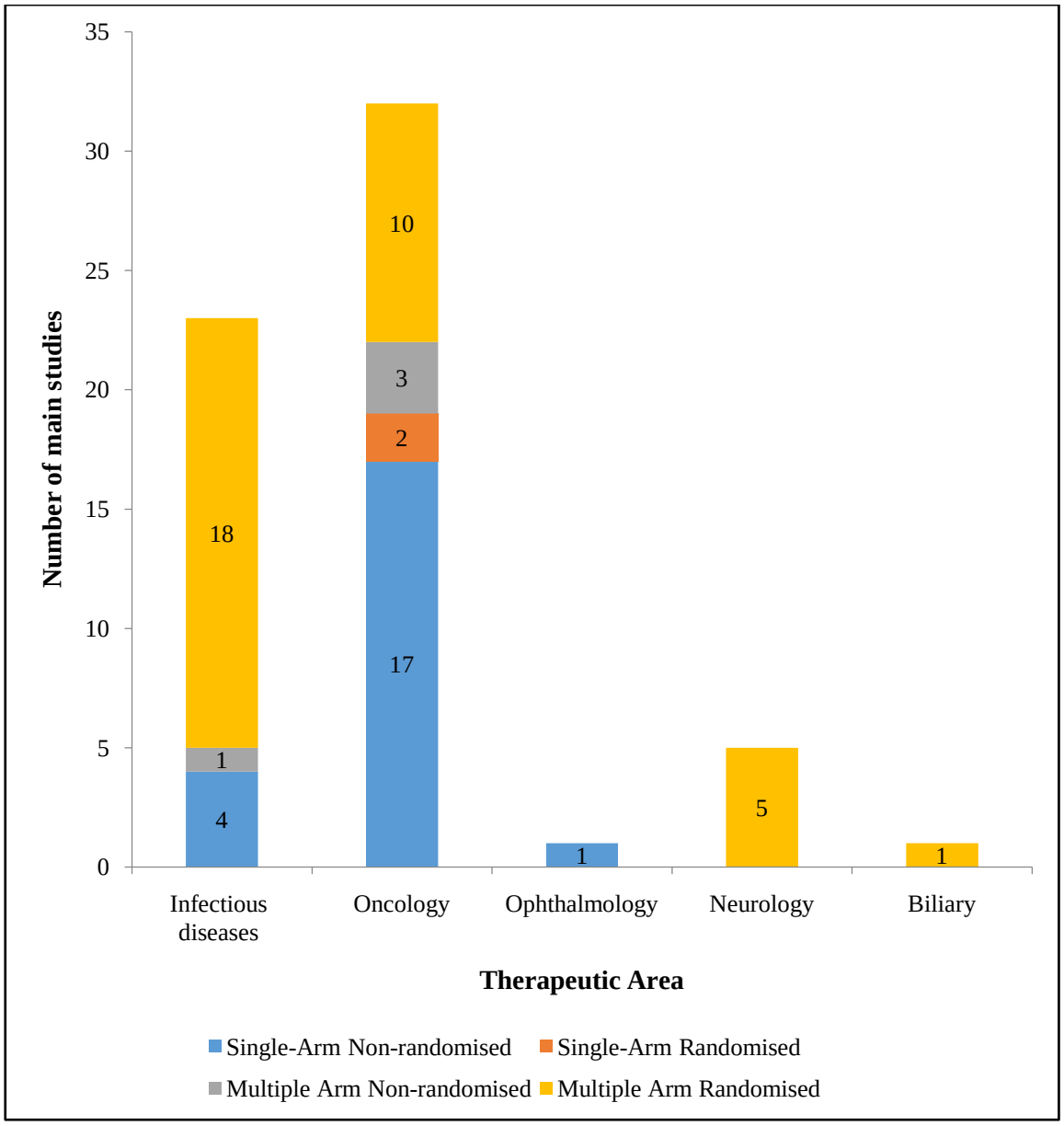

Figure 3.14 Pivotal study designs according to therapeutic areas (n=62)

Thirty-seven pivotal studies were not blinded studies, followed by 19 which were blinded (Figure 3.15).

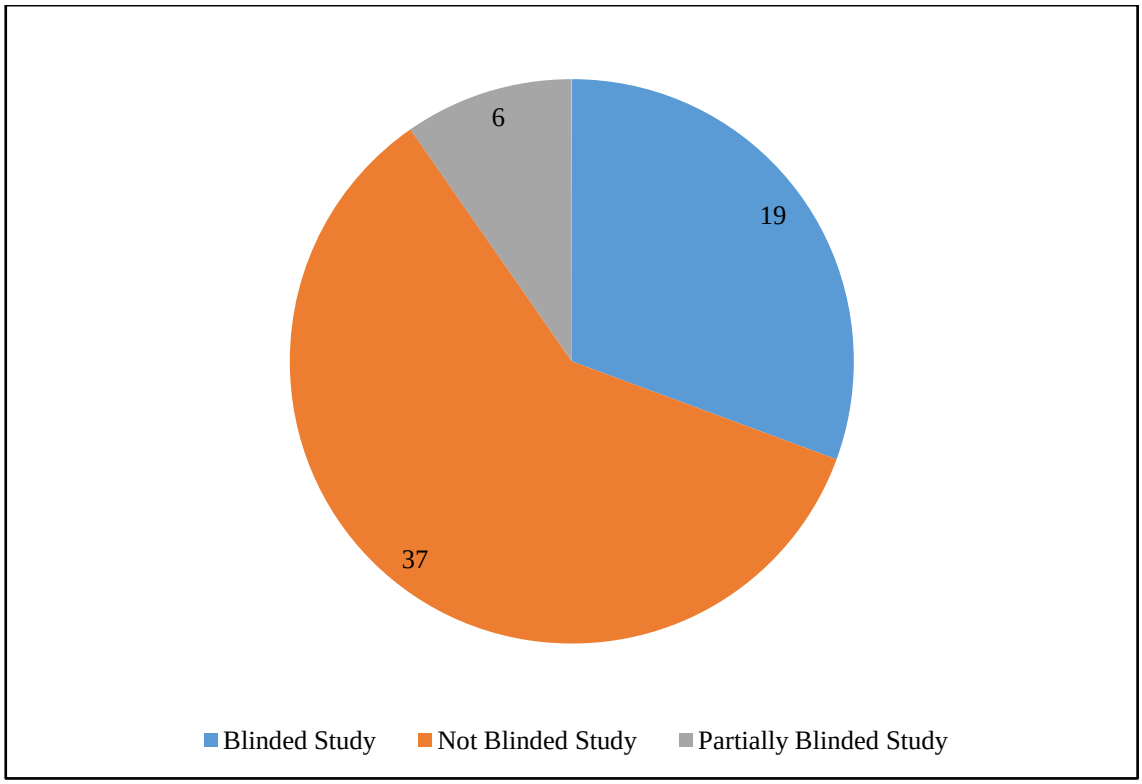

Figure 3.15 Blinding of pivotal studies (n=62)

Eleven out of 23 pivotal studies performed for products indicated for infectious diseases were non-blinded studies. Blinding was also not used for 25 pivotal studies out of 32 in the oncology area and 1 in the ophthalmological area. Blinded studies were performed for 7 products for infectious diseases and 6 oncology products. In the neurological and biliary therapeutic areas only blinded studies were used. Partially blinded studies were presented for 5 products for infectious diseases and 1 oncology product.

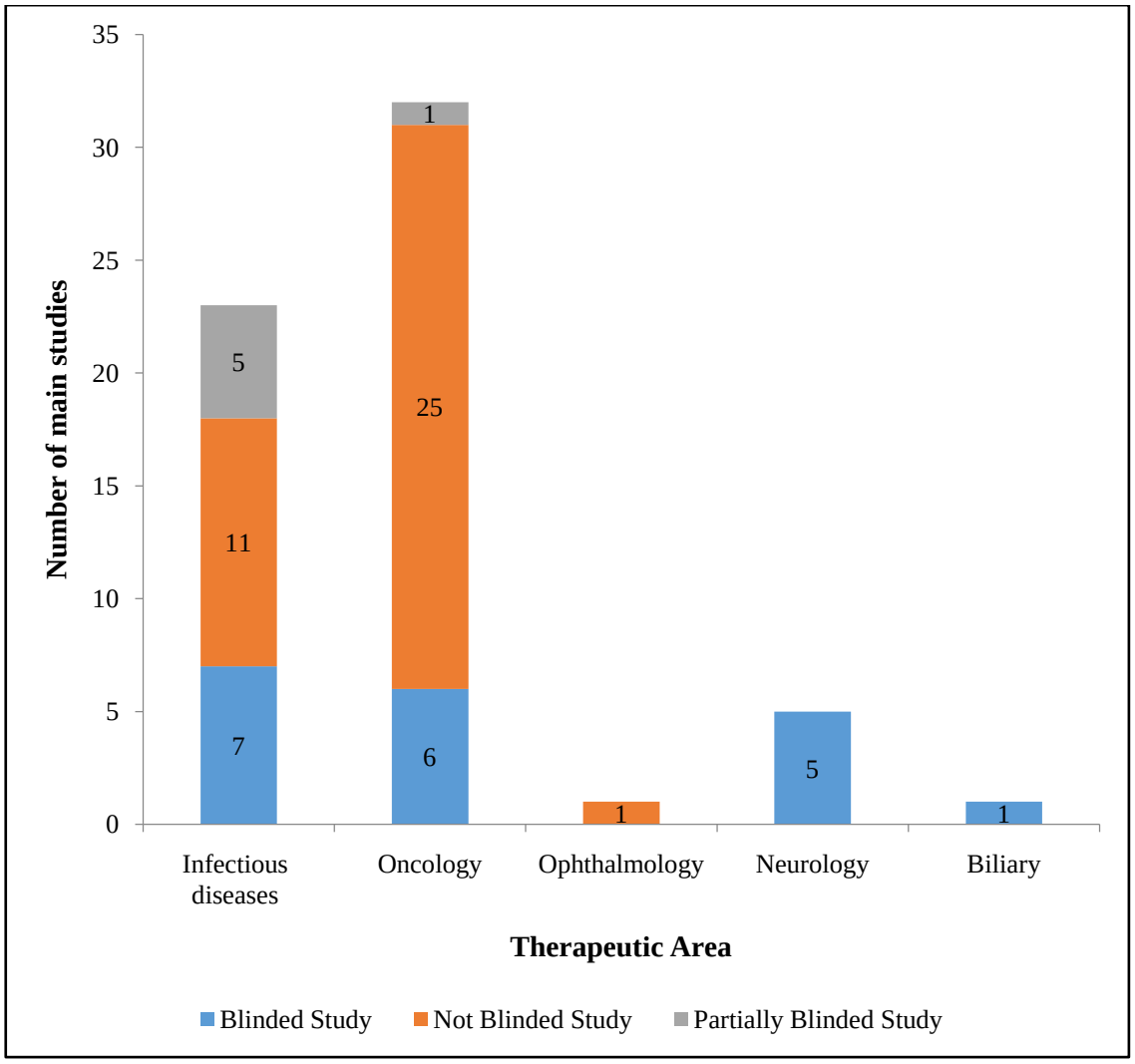

Figure 3.16 Blinding of pivotal studies according to therapeutic area (n=62)

Sample sizes used in these pivotal studies varied from 12 to 3263 patients. Due to the type of conditions being treated with products authorised through conditional approval, sample sizes were limited up to 722 patients with only 1 product exceeding 722 patients (Figure 3.17). This was the pandemic influenza vaccine H5N1 MedImmune with a sample size of 3263 patients enrolled in a phase III study. Forty five per cent (n=28) of the studies had a sample size between 100 to 149 and 200 to 249 patients. The larger sample sizes (> 250 patients) were observed in the infectious diseases and oncology therapeutic areas.

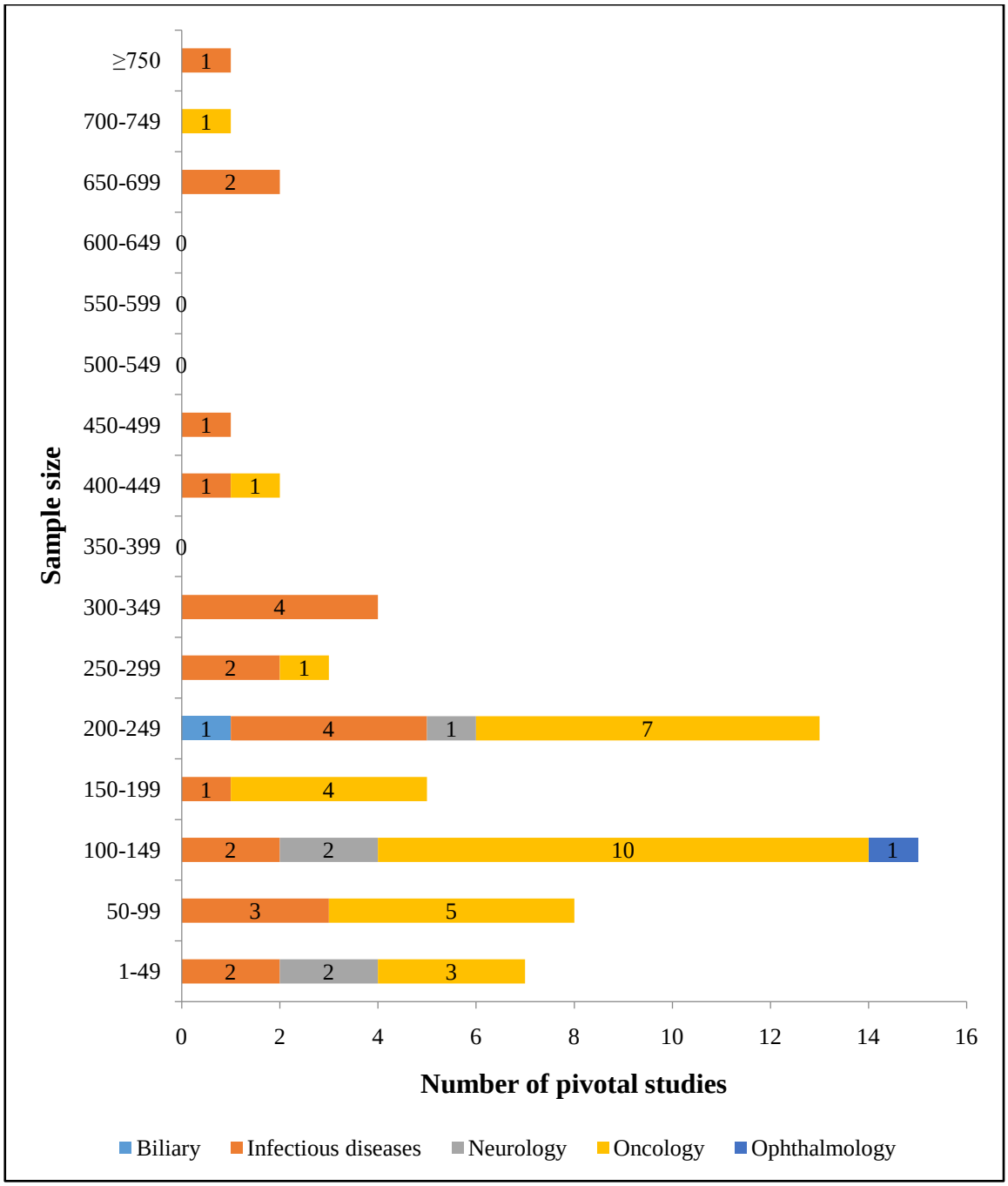

Figure 3.17 Sample sizes used in the pivotal studies according to therapeutic area (n=62)

The outcomes of the pivotal studies are confirmed through primary endpoints which provide the means of assessing whether a therapy is effective. The primary efficacy addresses the primary objective; is ascertainable in all patients; has demonstrated or

accepted relevance for the population and intervention(s) of the trial, and is sensitive to meaningful changes in a patient's health.

The types of primary endpoints used in the pivotal studies of conditional marketing authorisations are outlined in Figure 3.18. Thirty-two studies used ‘objective response rate’ (ORR) as the primary endpoint to show the positive outcome of the product, followed by ‘immunogenicity’ in 11 studies and ‘progression-free survival’ (PFS) in 9 studies.

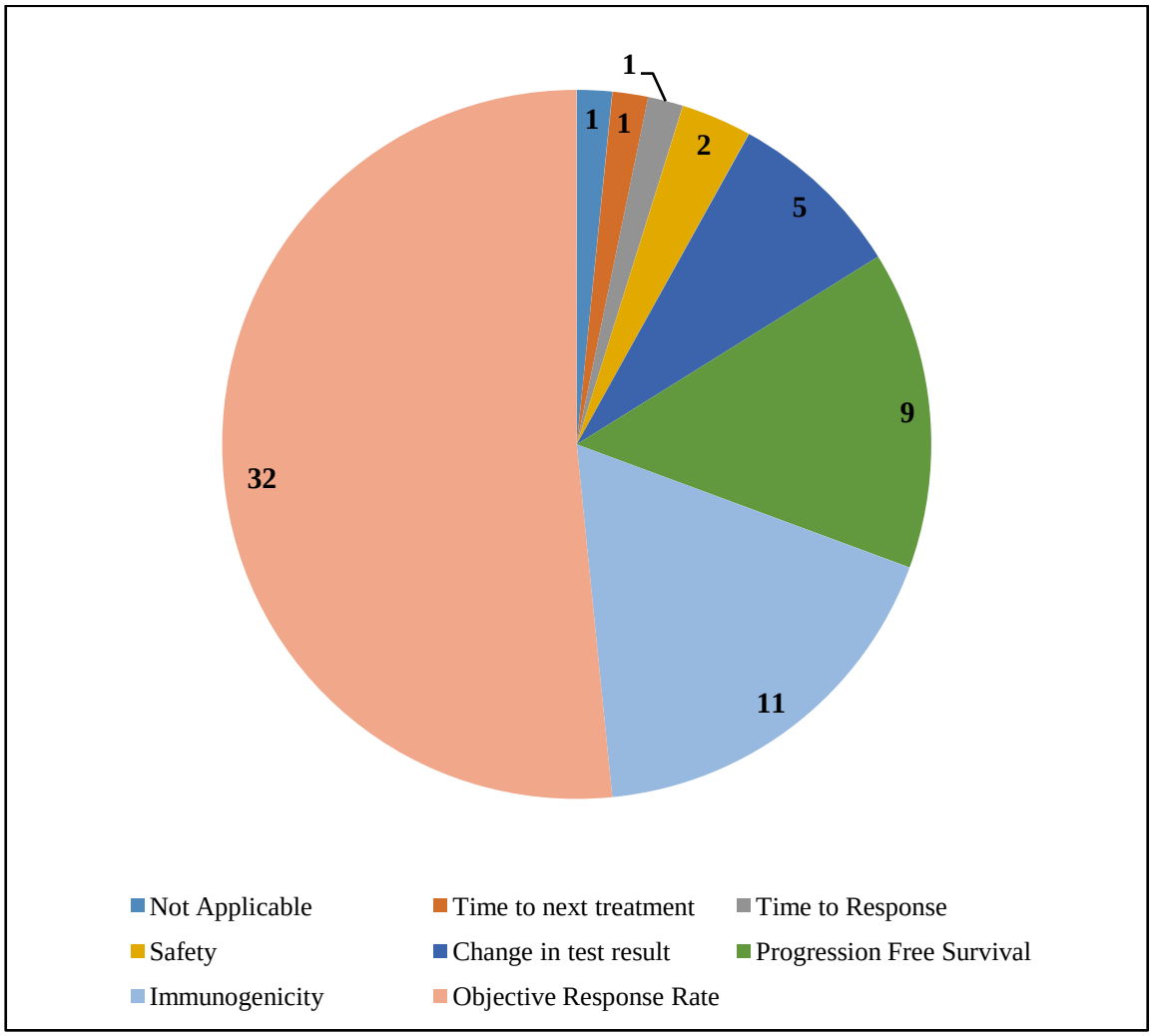

Figure 3.18 Types of primary endpoints used in the pivotal studies (n=62)

ORR (n=21) and PFS (n=8) were the most common endpoints used in the oncology therapeutic area (Figure 3.19). ORR (n=4) was also the main primary endpoint chosen for products indicated for neurological diseases. On the other hand in studies for products indicated in infectious diseases ORR (n=7) and 'immunogenicity' (n=11) were chosen as chosen primary endpoints.

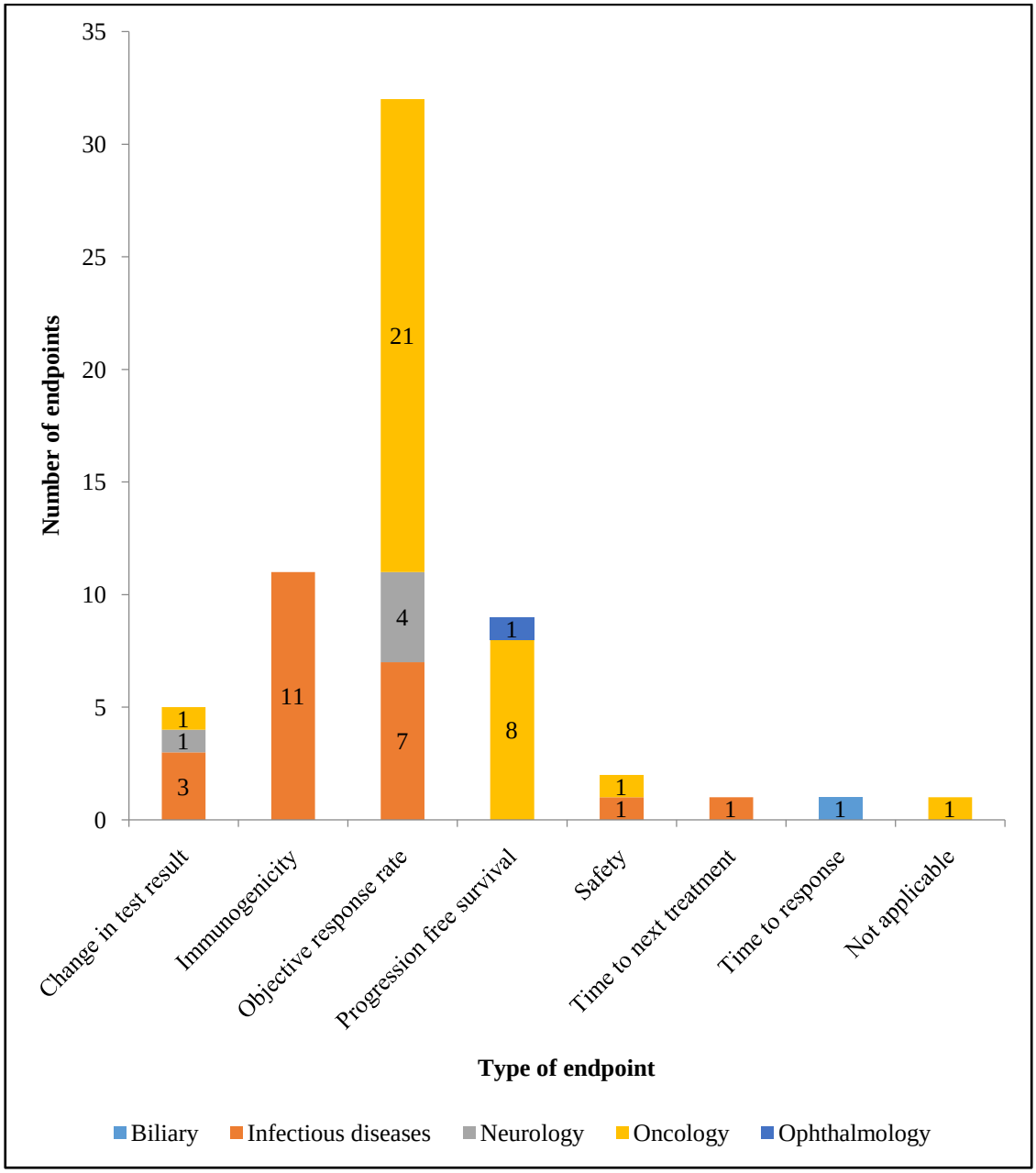

Figure 3.19 Types of primary endpoints used in the pivotal studies according to therapeutic area (n=62)

3.4.2.2 Pivotal studies supporting authorisations under exceptional circumstances

Thirty medicines were granted authorisation under exceptional circumstances from 2001 to 2016. When reviewing the licensing status of the medicines during submission of the initial application as detailed in the EPAR (Figure 3.20), it was noted that 16 out of 30 medicines were previously licensed in the USA (n=8) and in the EU (n=8). Fourteen of the medicines licensed under exceptional circumstances were not licensed in any country at the time of submission of the application.

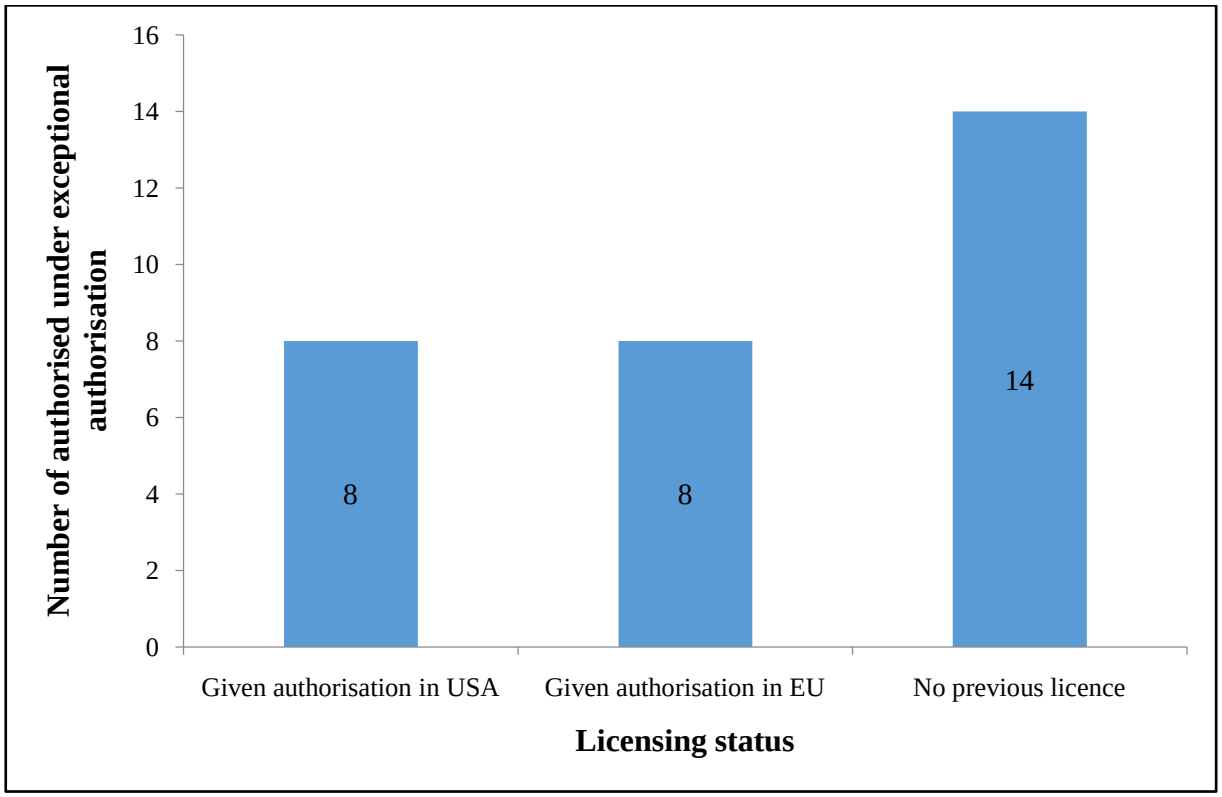

Figure 3.20 Licensing status of medicines granted authorisation under exceptional circumstances at the time of submission of initial application (n=30)

Forty-five phase II or phase III pivotal studies were used for the authorisation of the 30 authorisations under exceptional circumstances. Eighteen of 45 pivotal studies were phase II (including phase I/II) and 14 studies (were phase III (including phase II/III). Phase details of 13 pivotal studies were not specified in the EPAR (Figure 3.21).

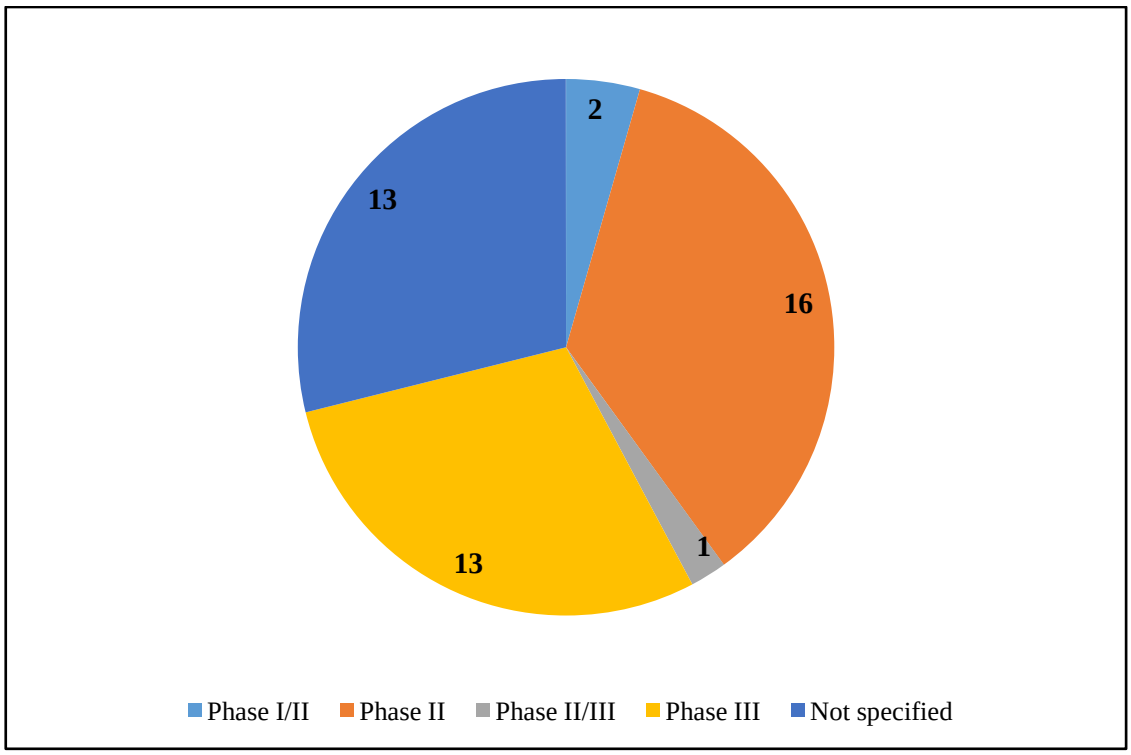

Figure 3.21 Pivotal studies identified in assessment of applications for authorisations granted under exceptional circumstances according to phase (n=45)

In the largest therapeutic areas, oncology (n=8), infectious diseases(n=6) and alimentary tract and metabolism (n=1) pivotal studies were Phase II studies (Figure 3.22). Two pivotal studies for products indicated in infectious diseases, 1 pivotal study for oncology products 2 pivotal studies for products indicated for alimentary and metabolism, were phase III studies. These results do not take into consideration the phases of pivotal studies not specified in the EPAR.

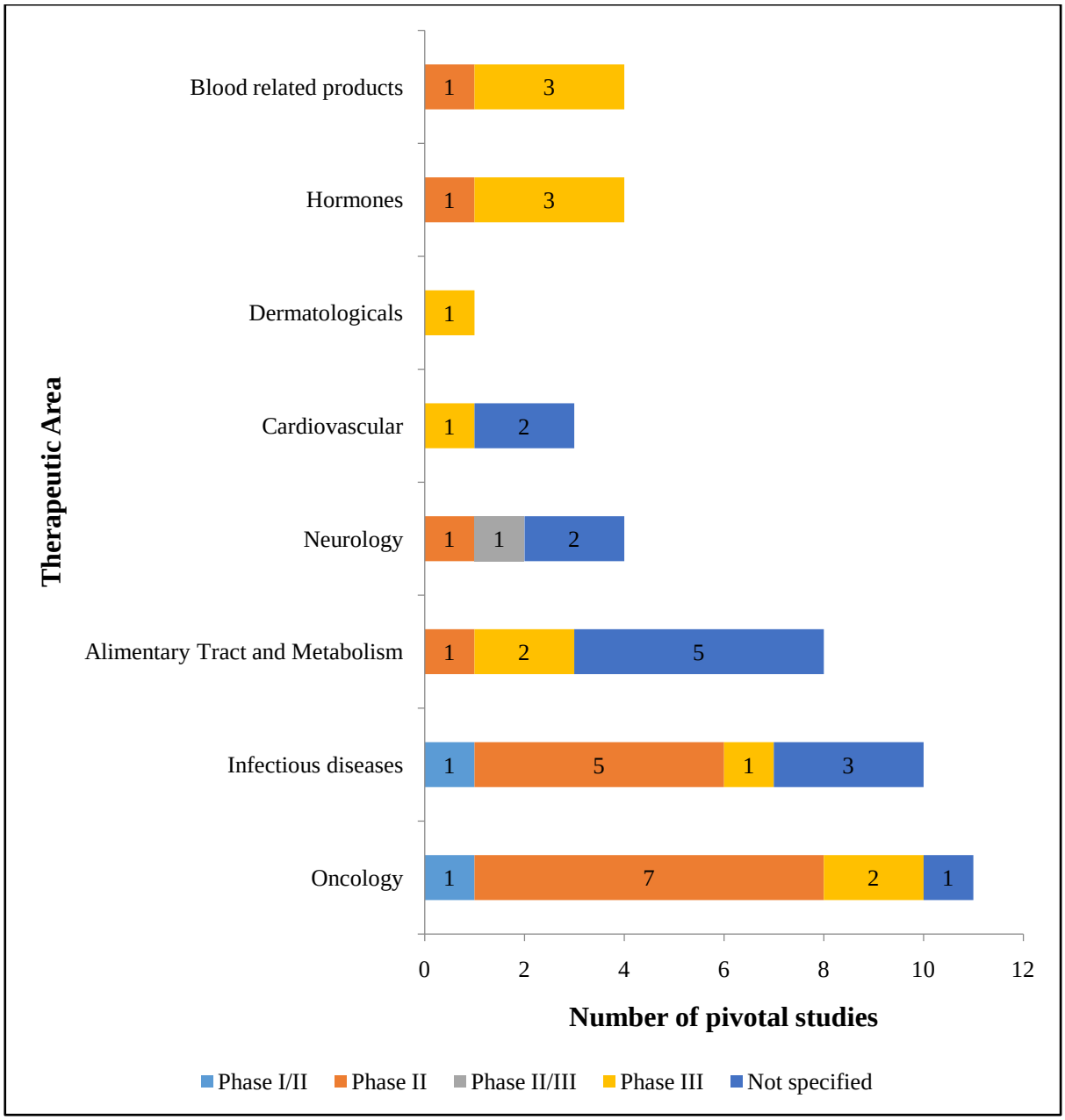

Figure 3.22 Distribution of phases of pivotal studies according to therapeutic area carried out for medicines granted exceptional authorisation (n=45)

Sample size used in these pivotal studies ranged from 8 to 2280 patients. Confirming the rarity of the conditions being treated with medicines granted authorisation under exceptional circumstances, 33 pivotal studies used sample sizes limited to not more than

199 patients (Figure 3.23). In 15 of the 45 pivotal studies, paediatric patients were included.

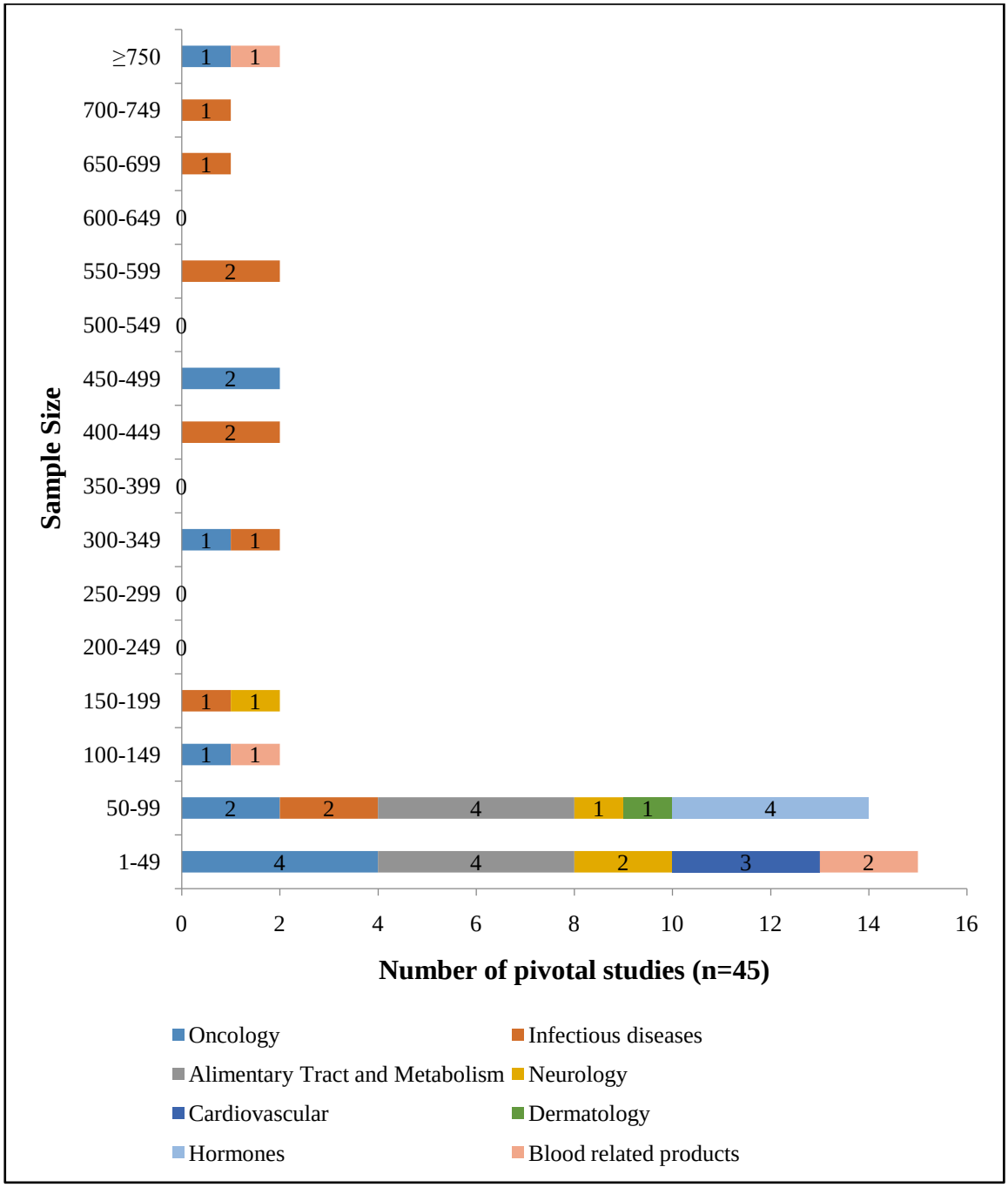

Figure 3.23 Sample sizes used in pivotal studies of medicines granted exceptional authorisation according to therapeutic area (n=45)

Thirty of 45 pivotal studies were multiple arm studies, whereas 10 were single-arm studies (Figure 3.24). Study designs of 5 pivotal studies were not specified in the EPAR. Twenty-one studies were randomised, whilst 15 studies were non-randomised. Details of the randomisation of 9 studies were not specified in the EPAR.

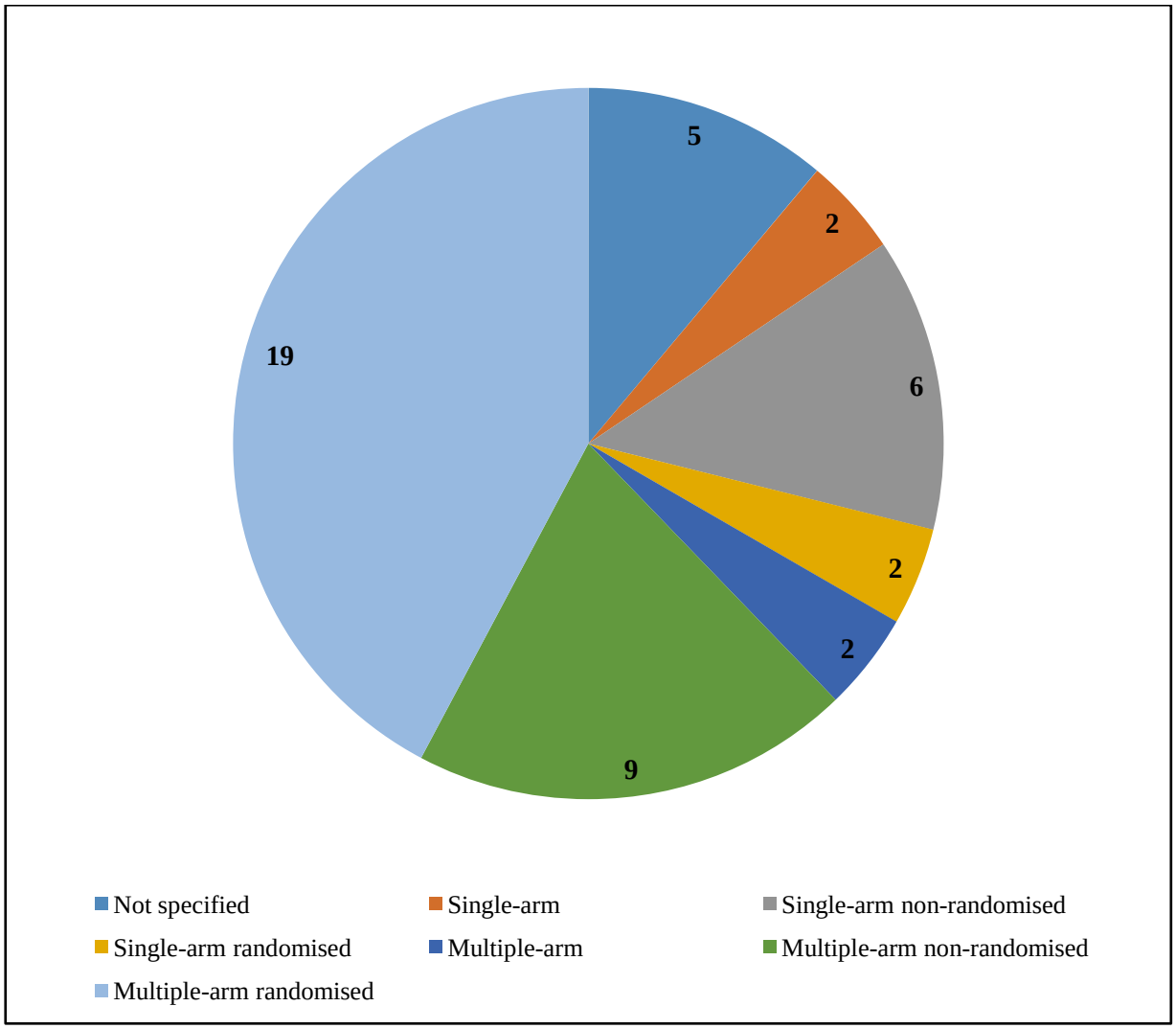

Figure 3.24 Study designs of pivotal studies (n=45)

No specific pattern in the study design used according to therapeutic area was observed. Use of multiple-arm studies dominated in all therapeutic areas except cardiovascular where only single-arm studies were used (Figure 3.25).

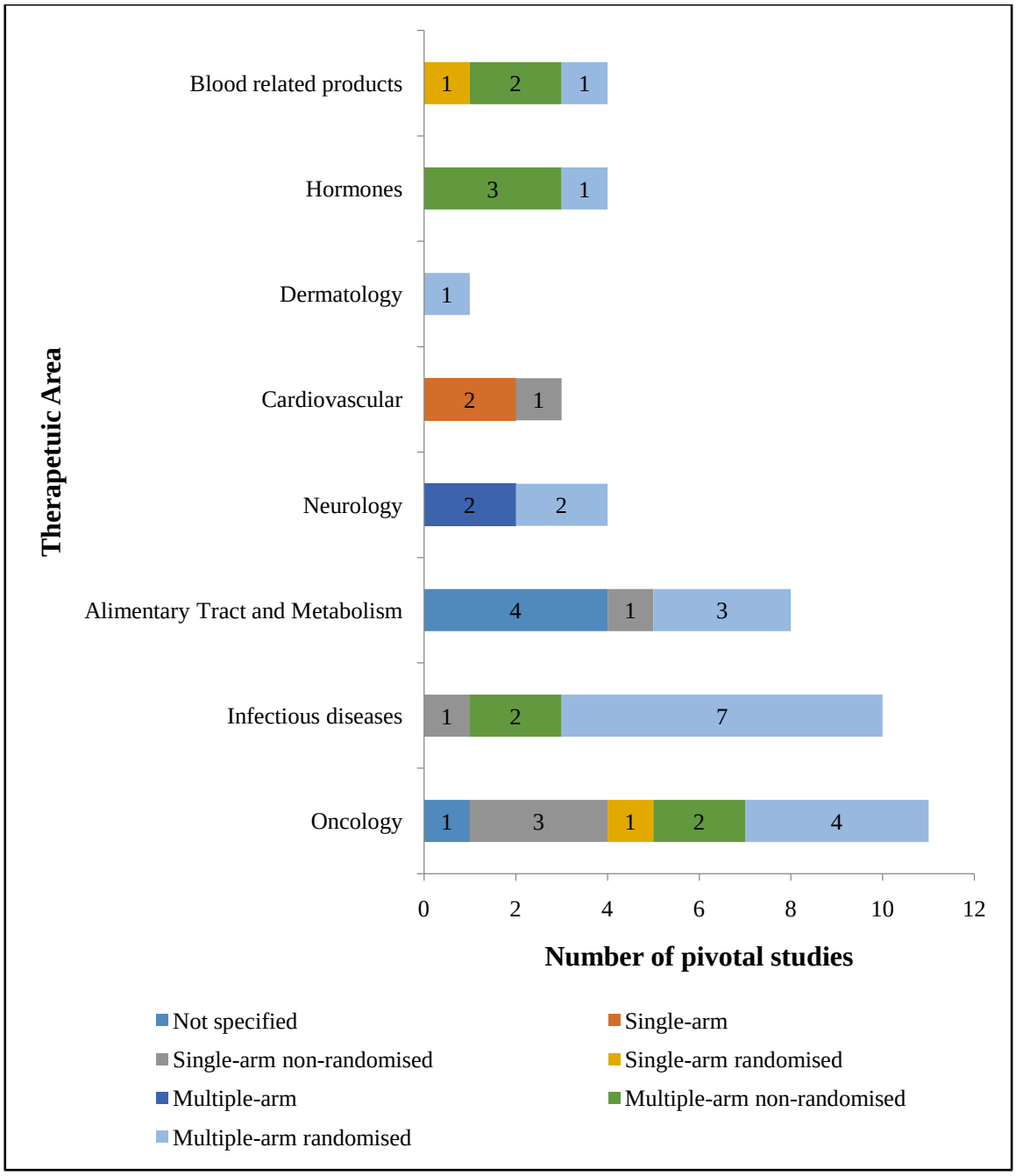

Figure 3.25 Pivotal study designs according to therapeutic area (n=45)

Twenty-six pivotal studies were not blinded studies, followed 15 pivotal studies which were blinded studies (Figure 3.26).

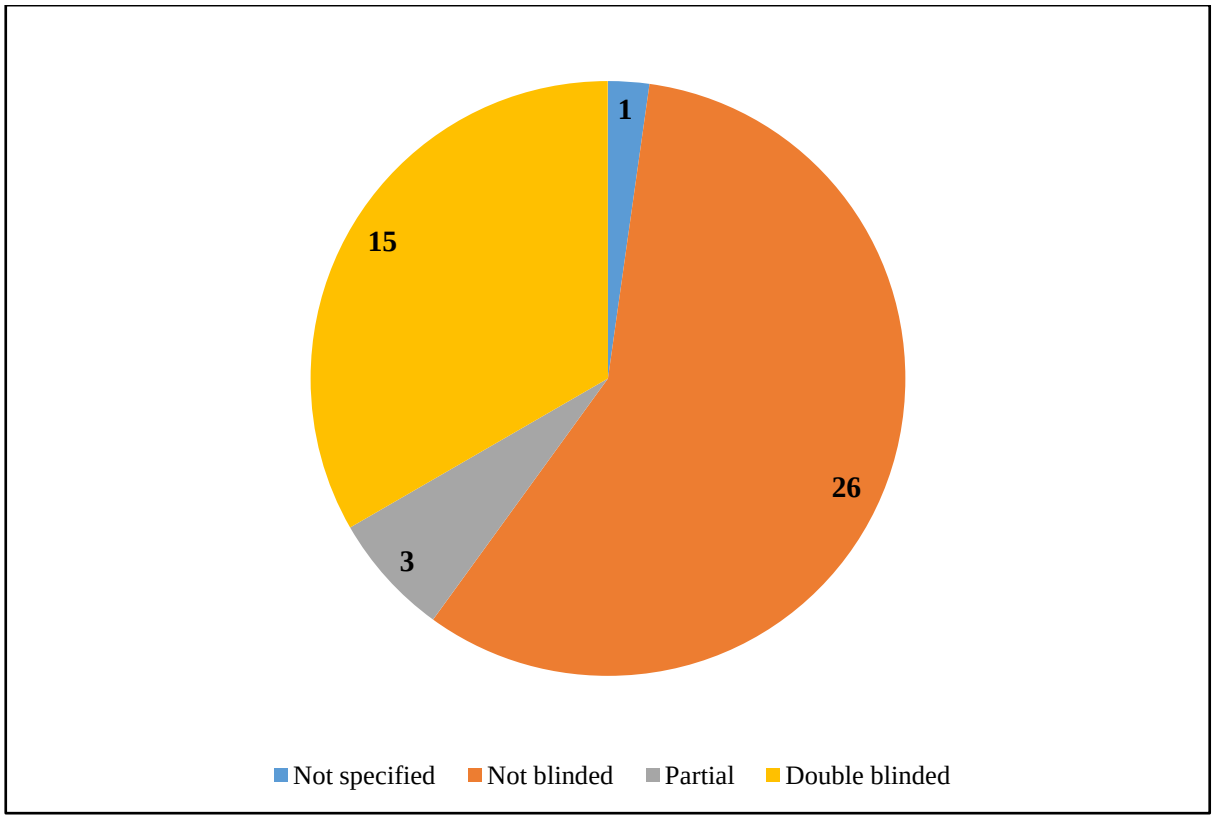

Figure 3.26 Blinding of pivotal studies (n=45)

In the 45 pivotal clinical studies, 63 primary end-points were used. Fourteen pivotal studies used 2 or 3 primary endpoints in the study design (Figure 3.27). Sixteen studies used ‘change from baseline’ as the primary endpoint to show positive efficacy of the product. This is followed by ORR in 13 studies, ‘immunogenicity’ in 9 studies, ‘complete response’ in 8 studies and ‘safety’ in 8 pivotal studies.

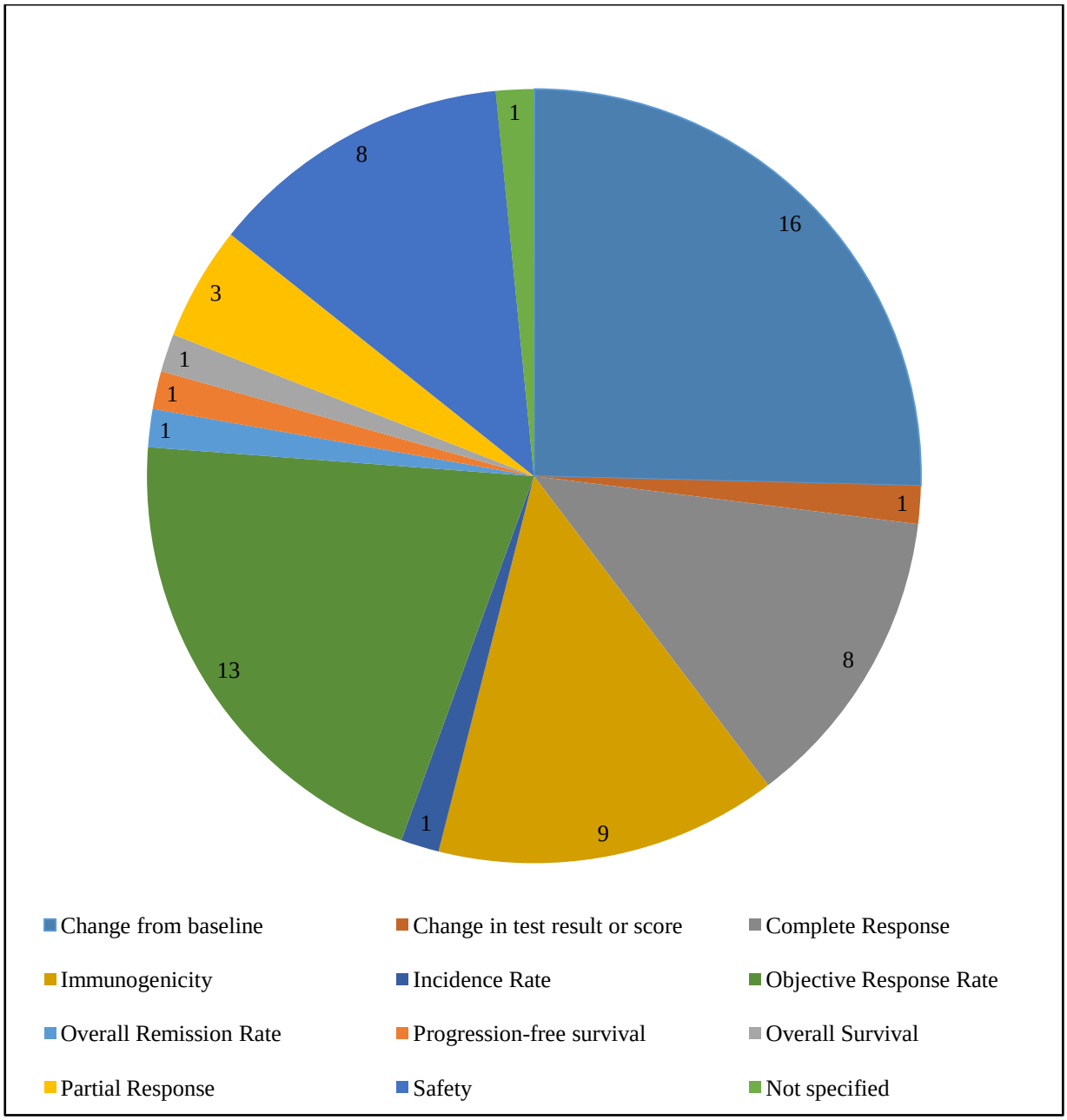

Figure 3.27 Types of primary endpoints used in the pivotal studies (n=63)

'Change from baseline' was a primary endpoint used in all therapeutic areas, except dermatology and infectious diseases (Figure 3.28). The main primary endpoint used in oncology area was 'complete response' (n=6), 'immunogenicity' in the infectious diseases area (n=9) and 'change from baseline' in alimentary tract and metabolism (n=8).

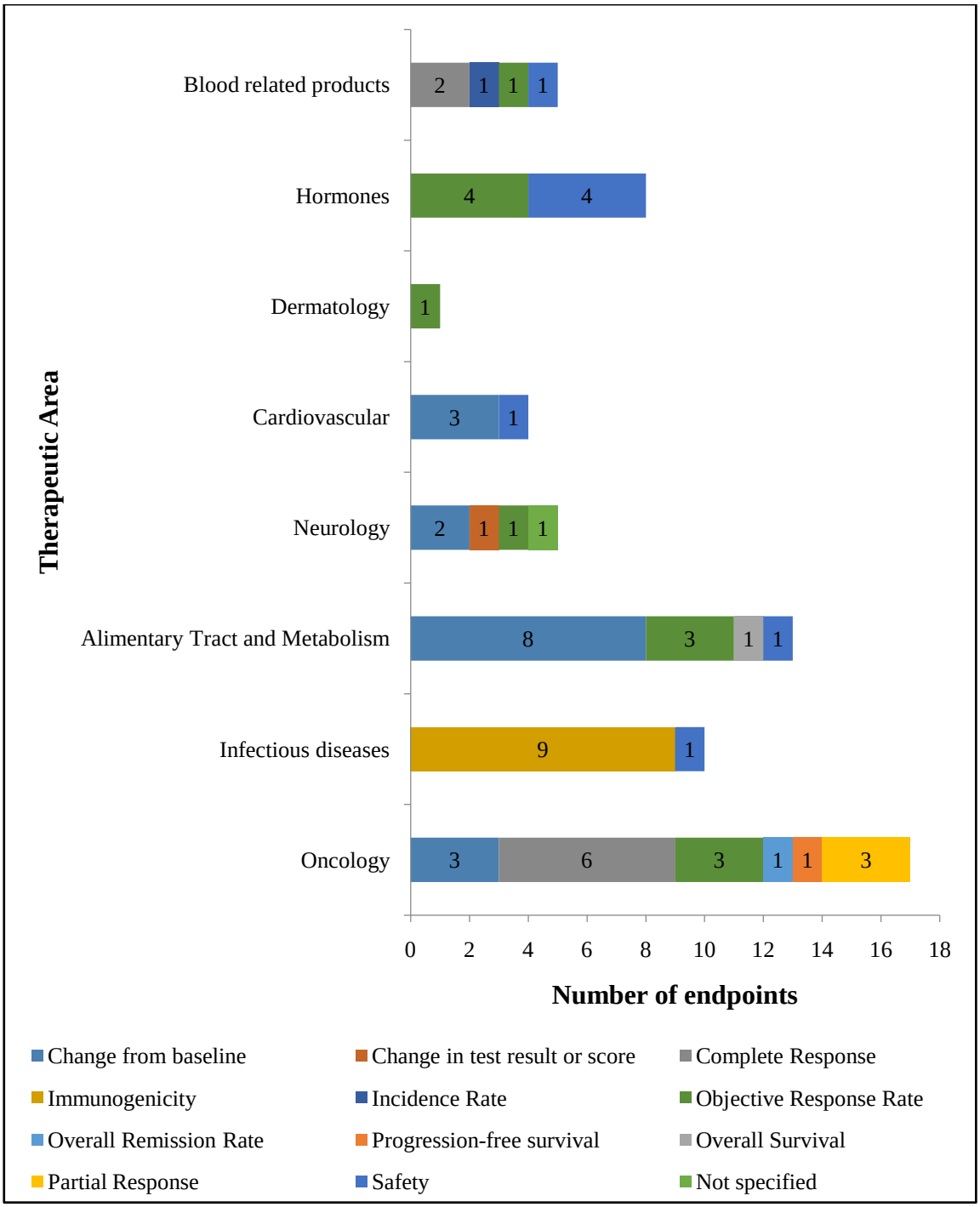

Figure 3.28 Types of primary endpoints used in the pivotal studies according to therapeutic area (n=63)

3.4.2.3 Clinical development programmes

The pivotall studies performed during development of medicinal products granted a CMA or authorisation under exceptional circumstances were documented in clinical development programmes (Appendix 2). Due to time limitations and a limited number of medicinal products in certain therapeutic areas, clinical development programmes were documented for the oncology therapeutic area for comparison purposes.

3.4.2.4 Specific obligations

For the 35 medicines granted a CMA, a total number of 108 specific obligations have been imposed, while for the 30 medicines granted authorisation under exceptional circumstances, a total number of 65 specific obligations have been imposed (Figure 3.29). Forty-five specific obligations imposed for CMA are requirements for submission of final results of ongoing clinical study on efficacy and safety. Forty-two specific obligations imposed for exceptional marketing authorisations are observational studies of post-authorisation efficacy (PAES) and post-authorisationsafety studies (PASS).

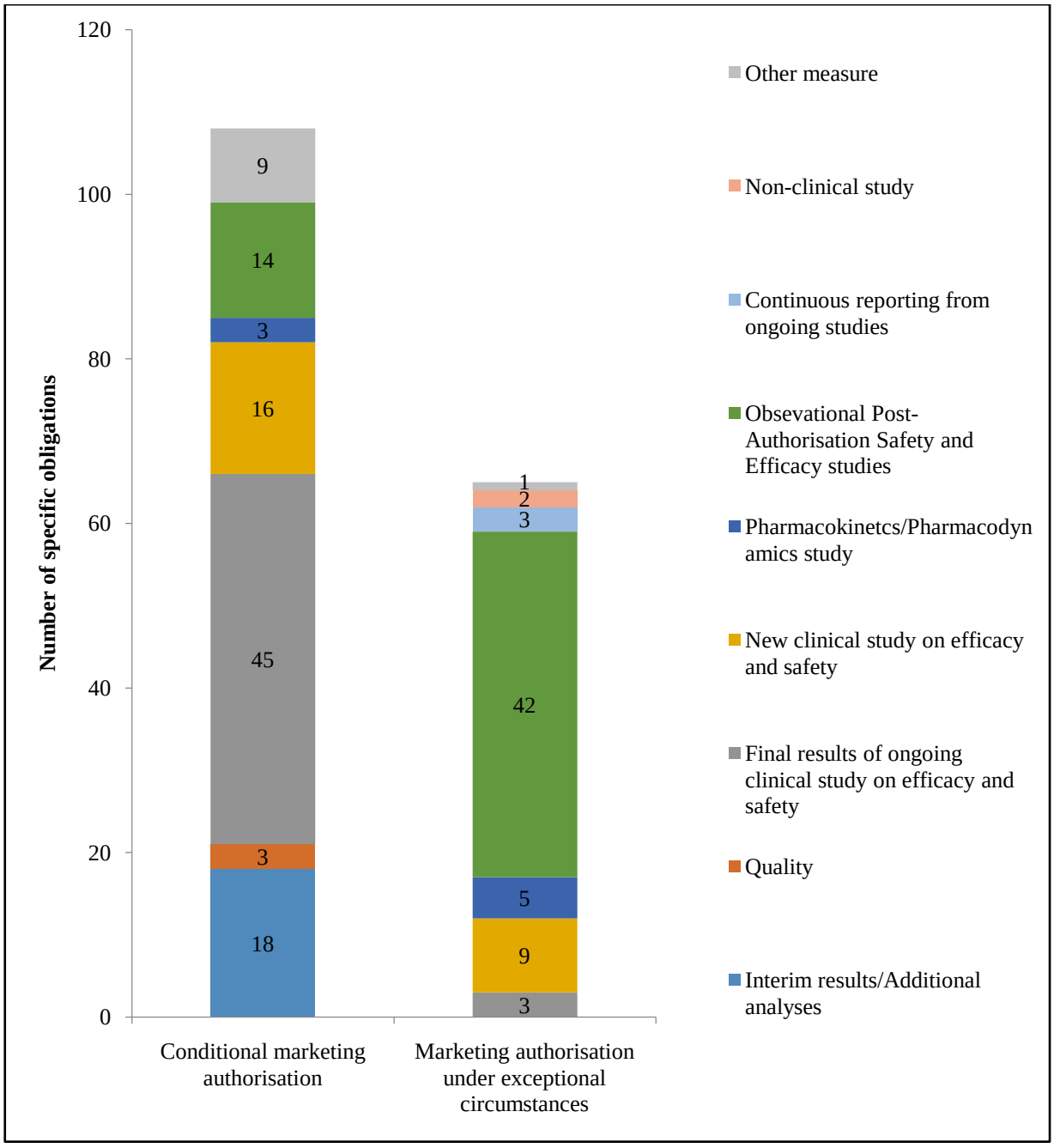

Figure 3.29 Types of specific obligations imposed

Up to December 2016, 55 specific obligations for CMAs were completed (Figure 3.30). Thirty-two are ongoing studies which were already initiated during the application process, whereas 3 ongoing imposed studies were completely new. Eighteen specific obligations were never initiated since the products were withdrawn.

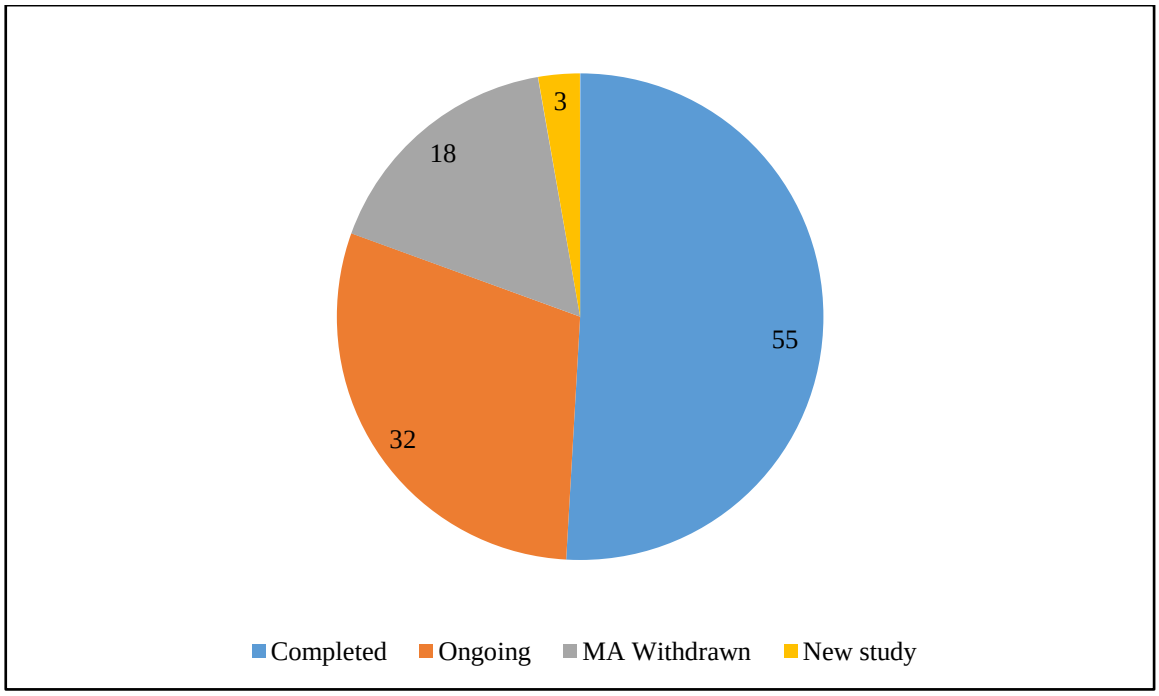

Figure 3.30 Status of specific obligations for conditional marketing authorisations (n=108)

Twenty-six out of 65 specific obligations for marketing authorisations granted under exceptional circumstances have a specific date of completion (Figure 3.31). Completion of all specific obligations is expected for 5 products (Figure 3.32).

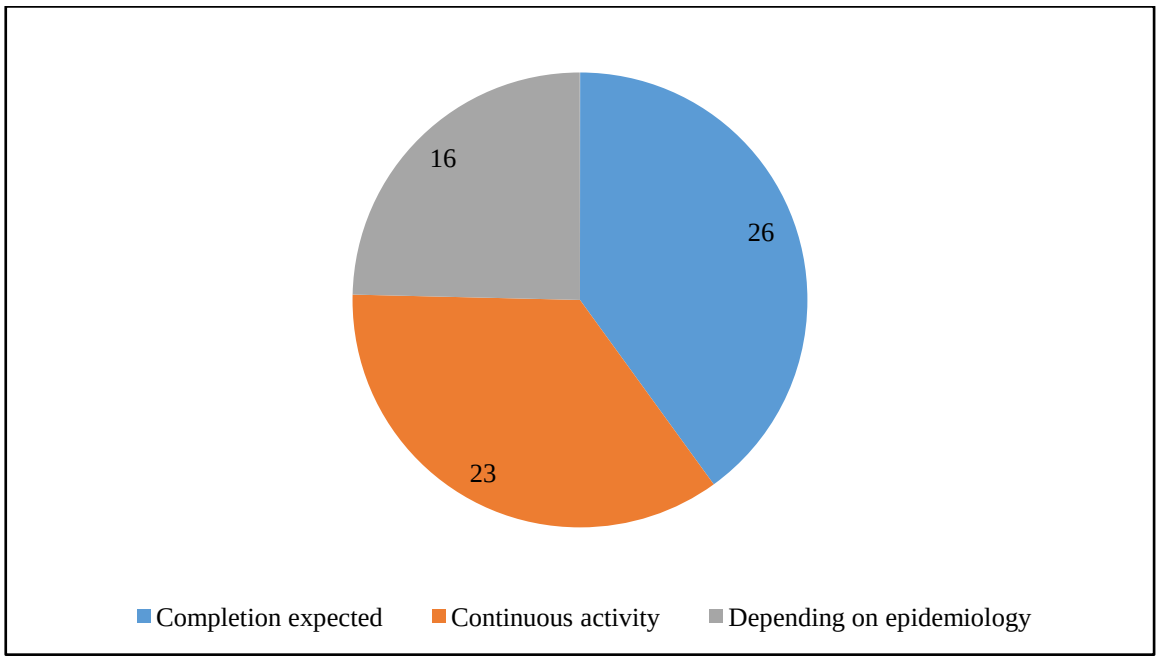

Figure 3.31 Types of due dates for specific obligations for marketing authorisations granted under exceptional circumstances (n=65)

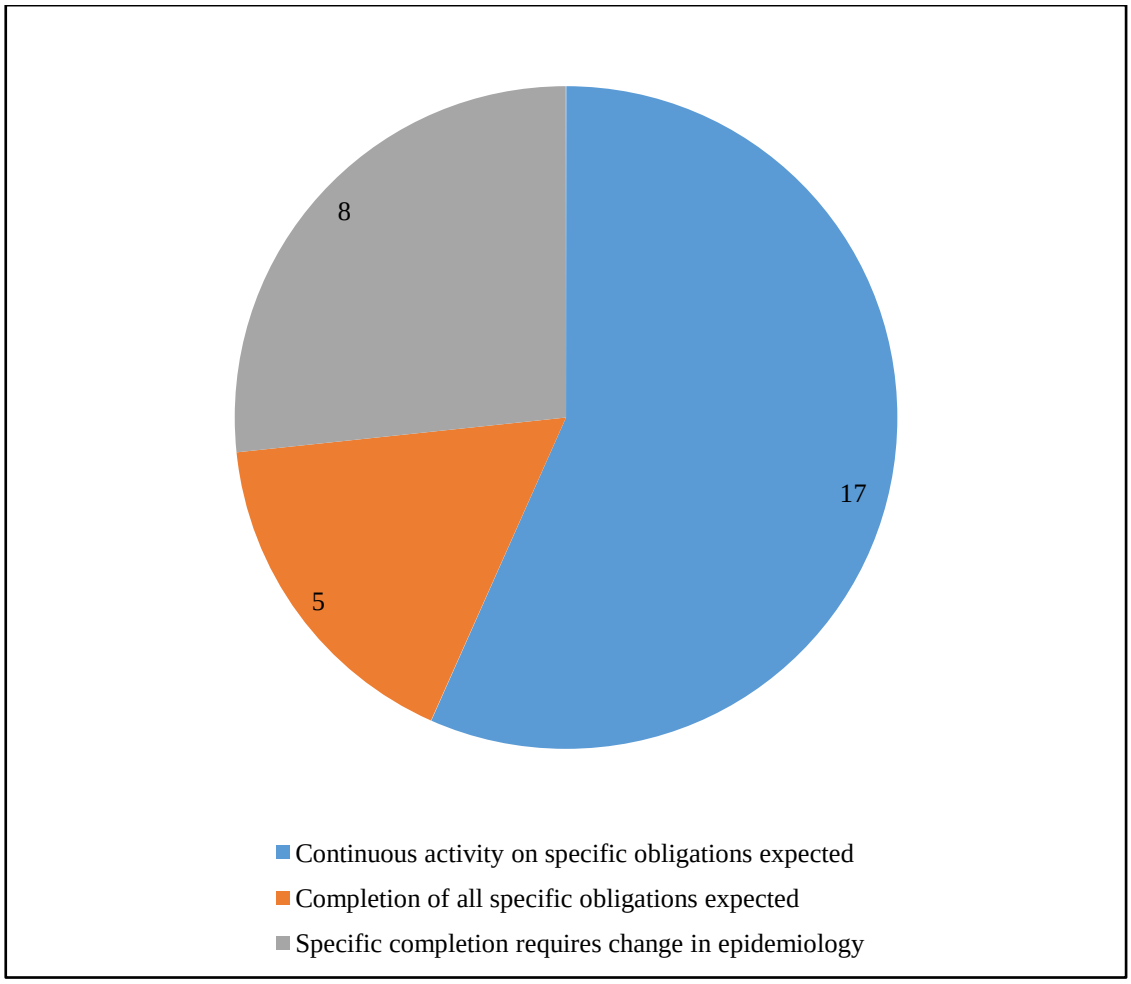

Figure 3.32 Expected completion of specific obligations for marketing authorisations granted under exceptional circumstances at product level (n=30)

Seventy-six CMAs and 50 authorisations granted under exceptional circumstances suffer no change to their specific obligation scope (Figure 3.33), indicating quality in the initial decision of the specific obligation. In terms of time of completion one can observe that there was no change in 73% (n=66) of specific obligations imposed for conditional marketing authorisations. With regards to authorisation granted under exceptional circumstances, there were 62% (n=16) specific obligations with a change in the due dates for completion. Minor changes can be taken as irrelevant but in 10 specific obligations the changes range from 2 to more than 5 years (Figure 3.34).

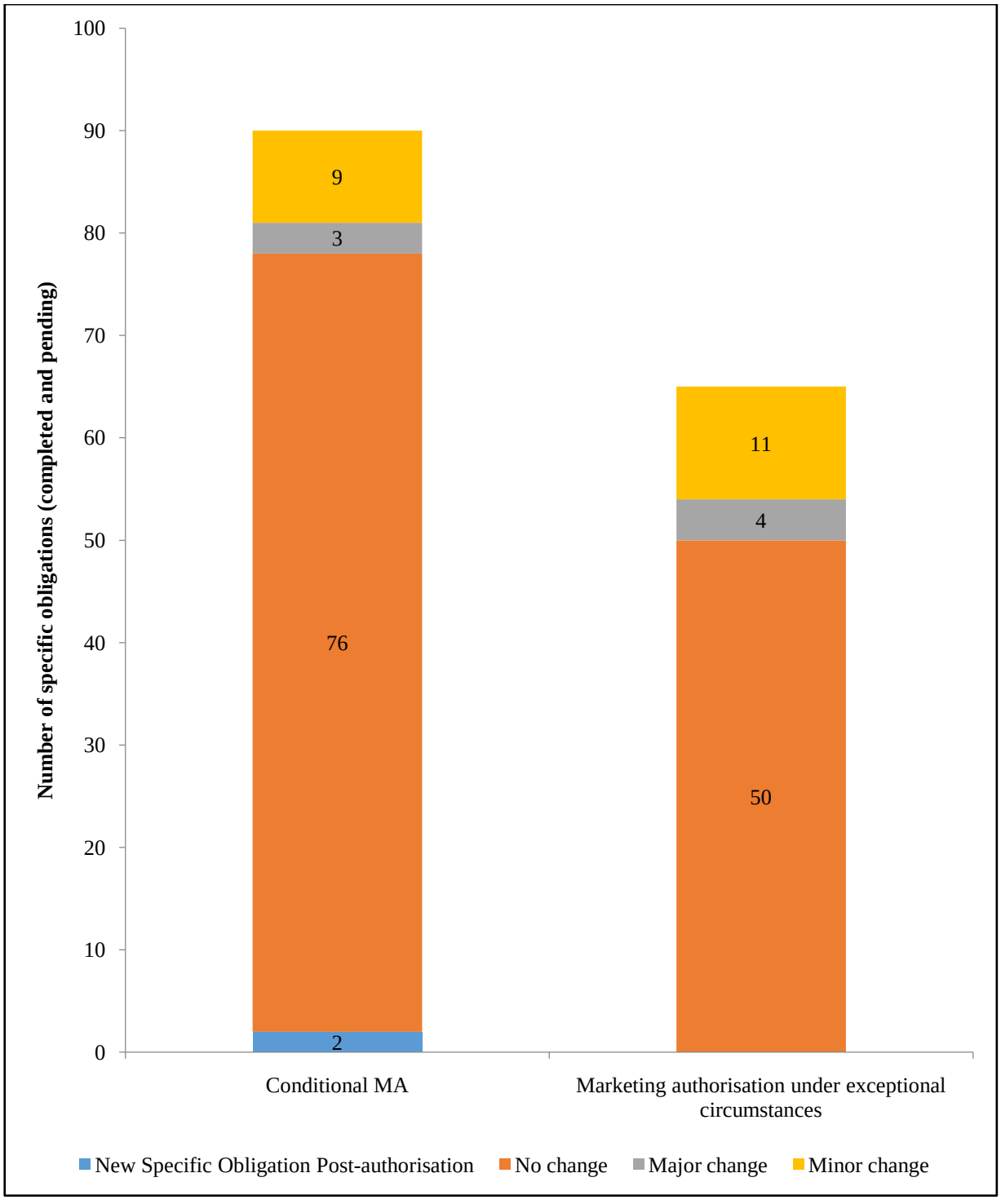

Figure 3.33 Changes to scope of specific obligations (n=173)

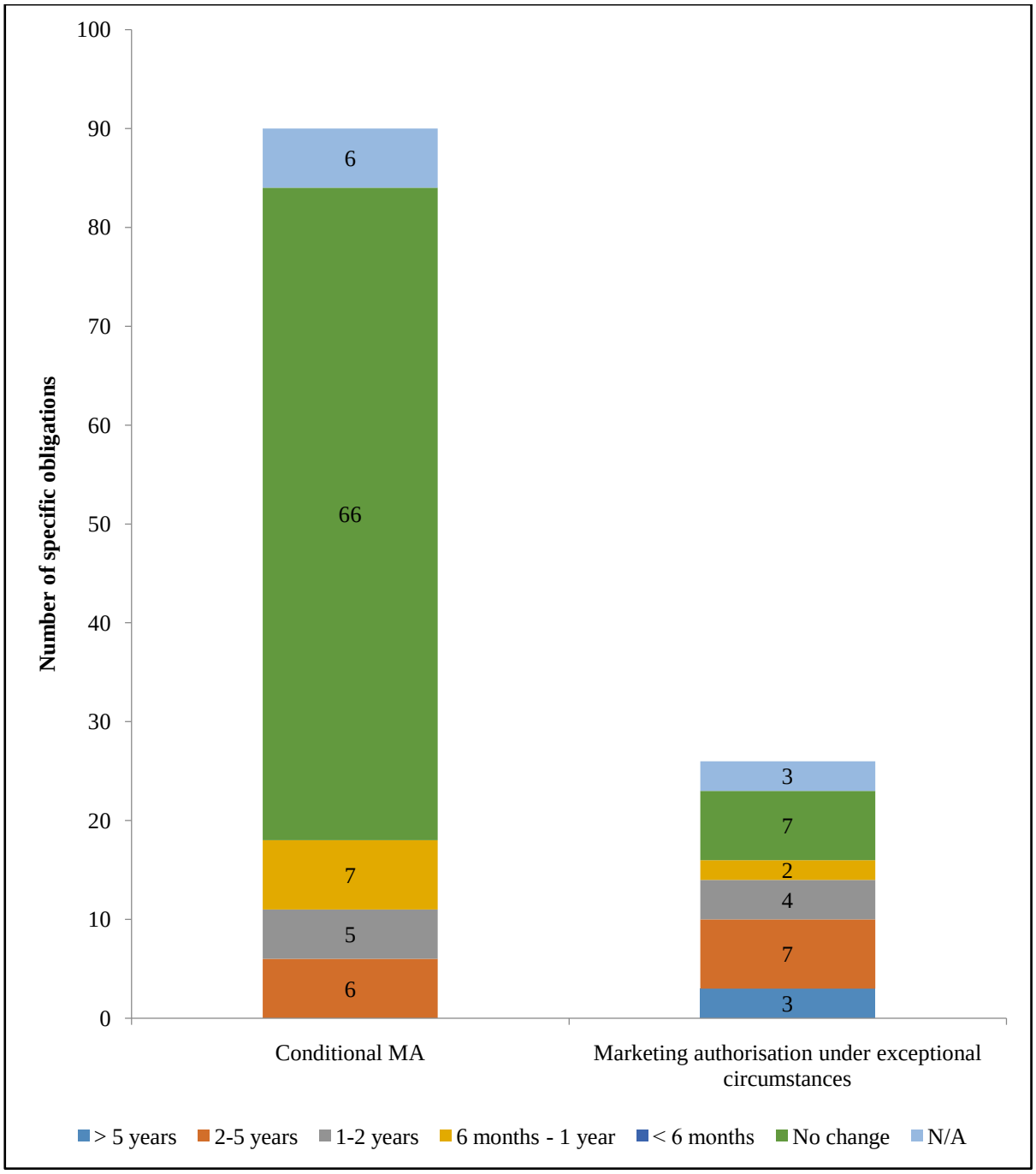

Figure 3.34 Changes to due dates for specific obligations with expected completion dates

3.5 Therapeutic coverage of innovative medicines in Malta

There were 822 CAPs registered with EMA licensed until June 2015. These products correspond to 522 unique ATC codes corresponding to 64 ATC codes according to the second level of the ATC code system (Appendix 3).

A total of 4707 nationally authorised medicines corresponding to 92 ATC codes according to the second level of the ATC code system had a valid authorisation in Malta in June 2015 (Appendix 4).

A total of 727 active ingredients were available for the patients free of charge as per applicable protocol were available through the Maltese NHS (Appendix 5).

The analysis showed that 322 unique ATC codes covered by centrally authorised products are not being provided in Malta through the NHS (Appendix 6).

The 322 unique ATC codes translate to 61% of active substances of CAPs that are not available in Malta. Diseases where treatments are not available lead to an unacceptable public health burden and imperative medical need. The listed indications of CAPs not available in Malta through the NHS were identified (Appendix 7).

A potential impact of the lack of treatment alternatives in Malta was identified to be more than 10% for 35 ATC codes, ranging from 10.68% for antithrombotic agents to 78.26% for other alimentary tract and metabolism products (Table 3.3).

Table 3.3 Percentage impact of the lack of treatment alternatives if centrally authorised products are not available

Full list of ATC Second Level Codes	Total number of authorisations in Malta	Total number of CAPs authorised	Number of CAPs not available in Malta	Percentage Impact (%)
A16 Other alimentary tract and metabolism products	**2**	**21**	**18**	**78.26**
L03 Immunostimulants	7	24	19	61.29
V04 Diagnostic agents	2	3	3	60.00
V10 Therapeutic radiopharmaceuticals	2	3	3	60.00
A08 Antiobesity preparations, excluding diet products	1	3	2	50.00
D03 Preparations for treatment of wounds and ulcers	1	1	1	50.00
M09 Other drugs for disorders of the musculoskeletal system	2	2	2	50.00
B06 Other hematological a gents	3	2	2	40.00
A10 Drugs used in diabetes	70	71	53	37.59
J07 Vaccines	43	39	28	34.15
R07 Other respiratory system products	7	3	3	30.00
A05 Bile and liver therapy	5	2	2	28.57
J05 Antivirals for systemic use	48	52	28	28.00
B03 Antianemic preparations	31	11	11	26.19
M05 Drugs for treatment of bone diseases	37	26	16	25.40
L01 Antineoplastic agents	176	102	63	22.66
V09 Diagnostic radiophar maceuticals	29	8	8	21.62
V08 Contrast media	15	4	4	21.05
L04 Immunosuppressants	36	41	16	20.78
V03 All other therapeutic products	35	14	10	20.41

Full list of ATC Second Level Codes	Total number of authorisations in Malta	Total number of CAPs authorised	Number of CAPs not available in Malta	Percentage Impact (%)
H01 Pituitary and hypothalamic hormones and analogues	34	9	8	18.60
B02 Antihemorrhagics	44	18	11	17.74
D06 Antibiotics and chemotherapeutics for dermatological use	21	4	4	16.00
S01 Ophthalmologicals	98	20	18	15.25
J04 Antimycobacterials	17	3	3	15.00
G03 Sex hormones and modulators of the genital system	67	19	12	13.95
G04 Urologicals	65	18	11	13.25
R06 Antihistamines for systemic use	46	7	7	13.21
N06 Psychoanaleptics	182	25	25	12.08
R03 Drugs for obstructive airway diseases	114	27	17	12.06
M04 Anti-gout preparations	15	2	2	11.76
N04 Anti-parkinson drugs	94	18	13	11.61
C02 Antihypertensives	21	5	3	11.54
C09 Agents acting on the renin-angiotensin system	254	35	32	11.07
B01 Antithrombotic agents	**66**	**37**	**11**	**10.68**

The lack of treatment alternatives of CAPs, including innovative medicines, in Malta was discussed with the MMA, DPA and CPSU (Appendix 8). With a population of around 419,000, it was highlighted by all entities that Malta's small size can lead to challenges in the pharmaceutical system, especially in areas of pharmaceutical innovation.

Factors which could contribute to the accessibility issues of medicines in Malta include:

1. Medicines not authorised in Malta
2. Medicines authorised in Malta but not marketed
3. Medicines authorised and marketed but unavailable due to shortages or supply chain issues
4. High prices of medicines
5. Dependence on importation with transportation costs increasing prices of medicines
6. Small domestic market which can result in disinterest by MAHs.

All entities have taken initiatives to address the problem of accessibility of medicines and ensure that the pharmaceutical system remains sustainable. Collaborations within the European network were highlighted as an important potential way to overcome issues of availability and affordability of medicines, particularly for a small member state such as Malta. Discussion on the way forward to ensure that innovation is present in the Maltese NHS, whilst maintaining a sustainable system included:

1. Provision of services to stakeholders by the MMA, such as provision of scientific advice, assessment of centralised procedures, increasing the number of European procedures with Malta as RMS and enhancing the work of the Medicines Intelligence and Access Unit
2. Joint HTA assessments
3. Innovative risk-sharing agreements or managed entry agreements
4. Joint procurement
5. Compassionate use programmes

3.6 Use of existing legislative tools to improve access to innovative medicines in Malta

Approval by the Licensing Authority for a product to be allowed in exceptional cases in line with Article 20 (1) of the Medicines Act, 2003, is being used as a regulatory tool to improve accessibility of medicines, particularly innovative medicines. In 2015 and 2016, 14 and 5 CAPs were imported through Article 20 (Table 3.4).

Table 3.4 Medicines imported through Article 20 in 2015-2016

2015	2016
Aprepitant 80 mg tablets	Iloprost 100mcg/ml injections
Aprepitant 125 mg tablets	Ribavirin 200mg tablets
Bevacizumab 25 mg/mL in 4 mL	Tocilizumab 20mg/ml concentrate for solution for infusion in 10ml vials
Bexarotene 75 mg liquid suspension/capsules	Lamivudine 50mg/5ml oral solution
Bortezomib 3.5 mg vials	Levetiracetam 100mg/ml oral solution
Bosentan 62.5 mg tablets	
Bosentan 125 mg tablets	
Daptomycin 500 mg injections	
Erythropoetin 1000IU	
Pegvisomant 10 mg vials	
Pregabalin 300 mg capsules	
Rituximab 100 mg injections	
Romiplostim 250 μg injections	
Trastuzumab 150mg injections	

Approval by the Licensing Authority for a product to be used as an unlicensed medicinal product on a named patient basis is also being used as a regulatory tool to improve accessibility of medicines. In 2015 and 2016, 2 and 3 CAPs were imported as unlicensed medicinal products (Table 3.5).

Table 3.5 Medicines imported for unlicensed use on a named patient basis in 2015-2016

2015	2016
Tocilizumab 20 mg/mL concentrate for solution for infusion in 10 mL vials	Cetuximab 100 mg / 20 mL vials
Zidovudine 10 mg/mL	Ribavarin 200 mg tablets
	Xalkori 200 mg capsules

Parallel trade[53] of CAPs is a legislative tool used to increase accessibility to medicines. Until 2015, there was no market for parallel distribution of CAPs in Malta and no notices for parallel distribution for Malta in the Maltese language were available.[54]

An investigation was conducted to identify underlying reasons for this discrepancy. The MMA held several meetings with stakeholders, such as Maltese parallel traders. The feedback received from these discussions indicated that apart from the small size of the market, the EMA administrative fees for parallel distribution may act as an additional disincentive to apply for a parallel distribution notice for Malta.

[53] European Medicines Agency (EMA). Parallel distribution [Online]. UK: EMA; 2016 [cited 2017 May 05]. Available from: URL: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000067.jsp&mid=WC0b01ac0580024594

[54] European Medicines Agency (EMA). The Parallel Distribution Register [Online]. UK: EMA; 2016 [cited 2017 May 05]. Available from: URL: https://fmapps.emea.europa.eu/paradist/

Through the MMA website, information on parallel distribution of CAPs was uploaded. Reference was made to the public register of parallel distribution on the EMA website, which provides up-to-date information on parallel distribution notices currently held by EMA.

Where a product already includes Malta as a member state of destination, the products can already be placed on the market in Malta through the listed parallel distributor/s for that product. Where the UK and/or Ireland is the member state of destination (pack is already in the English language), Malta could be added as a destination member state (where not already included) by the listed parallel distributor for that product.

Seven CAPs which were already authorised for parallel distribution in English language with Malta as a member state of destination were imported following the provision of information to stakeholders (Table 3.6). Importation of parallel distributed products in the English language has led to price reductions when compared to the products imported directly from the MAH.

Table 3.6 Products imported through parallel distribution in English language and their respective prices

Name of medication and pack size	Active ingredient	Price of non-parallel distributed product (€)	Price of parallel distributed product (€)
Bonviva® 150mg film-coated tablets x1	Ibandronic acid	46.36	36.90
Xenical® 120mg hard capsules x84	Orlistat	87.35	73.90
Evista® 60mg film-coated tablets x28	Raloxifene	35.90	32.90

Name of medication and pack size	Active ingredient	Price of non-parallel distributed product (€)	Price of parallel distributed product (€)
Suboxone® 2mg/0.5mg sublingual tablets x28	Naloxone, Buprenorphine	54.80	54.00
Suboxone® 8mg/2mg sublingual tablets x28	Naloxone, Buprenorphine	168.27	167.00
Plavix® 75mg tablets x30	Clopidogrel	44.40	23.50
Bexsero® suspension for injection x1	Meningitis B proteins	Never imported	175.00

The outcome of the lack of therapeutic coverage with CAPs in Malta was presented to the EMA to explore how parallel distribution of CAPs on the Maltese market could be improved including consideration of possible fee adjustments for the Maltese language. Following this request, EMA and the MMA launched a one-year pilot project for fee reductions for notifications of parallel distribution in the Maltese language from January to December 2016 (Appendix 9).

Fees comparable to the parallel import fees charged in Malta were introduced for a limited period as a pilot initiative. The applicable fees were reduced from €3,020 to €450[55] which is comparable to the fee charged by the MMA for its related parallel importation services for nationally authorised products.

[55] Ministry for Justice, Culture and Local Government. Subsidiary Legislation 458.46 Medicines Authority (Fees) Regulations [Online]. Malta: The Ministry; 2006 [cited 2017 May 05]. Available from: URL: www.justiceservices.gov.mt/LegalServicesSearch.aspx?type=lom&pageid=29

Meetings with stakeholders were held to inform them of this initiative. The one-year pilot project was also presented during the MMA Annual Stakeholder meeting held in September 2016.

The parallel distribution pilot initiative led to notifications for 5 centrally authorised products in the Maltese language (Table 3.7).

Table 3.7 Parallel Distribution notices issued in 2016-2017 in the Maltese language

Product Name/Active ingredient	Strength	Pack Size	Pharmaceutical Form	EU Number
Erbitux® (cetuximab)	5 mg/ml	1 vial	Solution for infusion	EU/1/04/281/003
Neulasta® (pegfilgratim)	6 mg	1 pre-filled syringe with needle guard	Solution for injection	EU/1/02/227/004
NeoRecormon® (epoetin beta)	4000 IU	6 pre-filled syringes	Solution for injection	EU/1/97/031/042
Firdapse® (amifampridine)	10 mg	100 x 1 tablet (unit dose)	Tablet	EU/1/09/601/001
Bexsero® (recombinant Neisseria meningitidis group B proteins)	50 µg/ 50 µg/ 50 µg/ 25 µg in 0.5ml	1 syringe	Suspension for injection	EU/1/12/812/001

The parallel distributors who applied for the above products are from Germany, Poland and Malta. The parallel distribution notice for Neorecormon® was submitted by the CPSU of the Department of Health in Malta.

The pilot project resulted in a positive impact with a decrease in ATC codes not marketed in Malta from 322 to 318, equating to an approximate 1.2% decrease in total ATC codes not marketed in Malta.

Further analysis of the listed indications of centrally authorised medicines (ATC code L01, L03, B03 and J07), where a lack of available treatment at a patient level in Malta, was carried out. This shows that a lack of available treatment at a patient level still exists as the 5 registered products do not change the percentage impact of lack of treatment alternatives reported in 2015 and therefore, the imperative public health need has not yet been resolved.

Through this pilot project initiative, patients requiring these products are now potentially benefiting from the initiative, with accessibility to the medicine required (Table 3.8).

Table 3.8: Number of patients benefitting from the pilot parallel distribution initiative

Product Name	Number of patients
Erbitux®	4
Neulasta®	Not yet in use
NeoRecormon®	2
Firdapse®	3
Bexsero®	Paediatric population (estimated initial target of 5,000 children)

The uptake of the pilot initiative by the local Maltese wholesale distributor, CPSU, has been slow. The approval took around 9 months for all the documentation to be in line with the requirements set by the EMA. A meeting with CPSU was held to understand the reason for this duration. The CPSU reported that there were numerous lessons learnt with the engagement process of Good Manufacturing Practice certified re-labellers/re-packagers, whereby a tender process had to be issued and adjudicated. This step has been a long process, in order to set specifications and issue the tender and adjudicate in line with Maltese procurement regulations. CPSU only managed to submit its first application at the end of November 2016. Furthermore, since this is a first application CPSU reported that labelling of immediate packaging in Maltese language has been challenging for the local stakeholders.

3.7 Dissemination of results

An abstract titled 'Evolvement of EU regulations on Innovative Medicines' was accepted for poster presentation at the 77th International Pharmaceutical Federation World Congress of Pharmacy and Pharmaceutical Sciences 2017, in Seoul, Republic of Korea, 10-14 September 2017 (Appendix 10).

CHAPTER 4

DISCUSSION

4.1 Impact of regulation on access to innovative medicines

The impact of development of innovative medicines is openly acknowledged, however but the development and launch of new medicines on the market require increasing efforts and costs (Paul et al, 2010). Improving patient access to innovative medicines is being discussed meticulously at European level, and the aim of this study was to assess the impact of the regulations on the access to innovative medicines. The regulatory system must ensure and facilitate introduction of efficacious and safe medicines to the European market.

A growing challenge faced by medicine regulatory agencies today is the responsibility of balancing the need for early market access to innovative medicines with the need for complete data on the benefits and risks of innovative medicines. Regulators have been criticised for authorising medicines on the market too early, with healthcare professionals requesting more comprehensive pre-marketing safety data (Garattini and Bertele, 2007; Nissen and Wolski, 2007) and more thorough assessment procedures (Eichler et al, 2008). HTA assessors and payers insist on the requirement for more and different, pre-marketing data, including information on relative efficacy and safety (Eichler et al, 2010). Such requirements would translate into lengthened pre-authorisation development programmes and longer time to authorisation and launch on the market.

On the other hand, there is increasing awareness of the humanitarian need to overcome delays in access to potentially life-saving medicines, which is demonstrated, for example, by the activities of an increasing number of patients' organisations (Kaplan et al, 2013; Mavris and Le Cam, 2012) such as European Organisation for Rare Diseases

(EURORDIS) and European Patients' Academy (EUPATI). According to patients' organisations, regulators should use more flexibility to facilitate innovation by lowering the barriers of market entry.

This study examined a regulatory perspective on the challenge of balancing early market access with uncertainty about benefit/risk profiles of new drugs. The regulator is responsible for the granting of a marketing authorisation which does not necessarily imply that the medicine is actually launched on the market and accessible to the patient. Treatment with innovative medicines would also require reimbursement decisions by the relevant National Health Service.

Regulatory decisions during review of applications submitted through one of the early access initiatives are taken under conditions of uncertainty (Eichler et al, 2008). For assessment of the benefit/risk balance, the overall level of uncertainty is associated with all the constituent uncertainties of safety and efficacy parameters (Curtin and Schulz, 2011). Uncertainty about safety may be even greater, as most studies for regulatory authorisation with early access tools are driven to show efficacy rather than safety (Martinalbo et al, 2016). Each regulatory decision entails a level of acceptable uncertainty about the benefit/risk assessment, below which regulators may be prepared to take a positive decision on the authorisation of a new medicine (Eichler et al, 2015).

Analysis of past regulatory decisions according to the selcted study design supports the concept that the level of acceptable uncertainty is not constant across all therapeutic indications. Regulators are generally in agreement to accept a higher level of uncertainty around the benefit-risk assessment for conditions with unmet medical need,

as opposed to less severe conditions. The positive opinion given to these medicines are based on a relatively small number of patients enrolled in clinical trials compared to non-life-threatening indications, or based on single-arm trials and/or surrogate endpoint information (Jones, 2001). Single-arm trials are generally considered to capitulate towards less robust information when compared to randomised controlled trials.

Authorisation of medicines in areas of high unmet need is moving towards life-cycle regulatory management. It is expected that medicines will increasingly be approved initially for small groups of patients who are expected to accrue the greatest benefit from the medicine in order to justify a positive benefit/risk balance in the presence of a limited safety database. For this approach, an unmet need for well-defined patients must be demonstrated and approved by regulators (Eichler et al, 2008). This direction is expected to stimulate pharmaceutical innovation and research for targeted and personalised therapies and to increase requirements of post-marketing studies, with imposition of specific post-marketing obligations, to continuously confirm the benefit/risk assessment. The post-marketing studies will address the detection of new adverse events and ensure re-assessment of efficacy under real-life conditions (effectiveness) and of treatment-eligible populations (Eichler et al, 2010).

Since the introduction of the CMA in 2006, there has been interest in this early access tool which resulted in 35 marketing authorisations over 10 years. The CHMP has assessed the benefits and risks of these innovative medicines and considered conditional application, when appropriate, as demonstrated by the number of successful authorisations. The CHMP has also assessed the benefits and risks of 30 innovative medicines which were granted exceptional marketing authorisations, addressing

conditions with unmet medical need. With the use of CMAs and marketing authorisations under exceptional circumstances, the European market has seen the launch of 33 orphan medicines and 27 new active substances.

The assessment of a CMA is based on less comprehensive data than that required for a full MA.[45] In 46% (16 out of 35) of the cases at the time of granting initial authorisation data, from at least one phase III study formed part of the main evidence. A decrease in completed phase III studies was noted in the past 3 years (Section 3.4.2.1). The decrease in completed phase III studies may show that the CMA is being applied for its intended use with medicines having less comprehensive data, and the medicines with complete evidence go through the 'standard' marketing authorisation application.

The types of pivotal study designs used for initial authorisation were open-label (60% - 37 out of 62), randomised (58% - 36 out of 62) studies measuring a pre-defined response rate as primary efficacy endpoint (52% - 32 out of 62). Differences between the therapeutic areas were observed, for example, for medicines used in oncology and ophthalmology, single-arm studies were more commonly used (52% and 100% respectively). Open-label studies were more common in oncology (78% - 25 out of 32) and ophthalmology (100% - 1 study) areas. Use of randomised trials provides more robust evidence since randomisation is a rigorous way of determining whether a cause-effect relation exists between treatment and outcome (Ciani et al, 2013). Use of single-arm studies is more challenging for regulators since these are usually used when RCTs are not feasible. This is usually the case when the population is too small due to the rarity of the condition or when there is compelling efficacy evidence in phase II exploratory trials. The authorisation process is taken on a case-by-case basis and is

normally driven by the results presented. In conditions for which treatment in not available, use of single-arm trials may be the only acceptable option for some patients. Use of open-label trials may also indicate the increase in involvement and awareness of the patients (Blader, 2005).

Increasing the approval rate is important to assess and understand the role of critical steps in relation to non-approval of conditional and exceptional authorisations. In order to decide on the marketing authorisation of a new medicine, CHMP defines and weighs benefits and risks by assessing the i) clinical outcome (efficacy and safety results) of the main studies and ii) clinical relevance of the results. The design and conduct of the development plan are considered to validate the clinical outcome. Each factor of the benefit-risk assessment should be considered when explaining whether a medicine is approved for human use or not. Results of the pivotal studies are the main data used for discussion of the benefit-risk balance of the medicines under assessment, which leads to a positive or negative CHMP opinion for authorisation.

In 52% of the cases (32 out of 62), the primary endpoint of the pivotal study was percentage of subjects reaching certain criteria for response, as defined in the protocol, classified as ORR. For example, 66% (21 out of 32) of the endpoints used in studies of oncology medicines were ORR. Oxnard et al (2016) published a study which concluded that ORR is an appropriate clinical endpoint to be used in oncology. Specifically, the authors concluded that their "data suggests that high ORR is an appropriate end point for single-arm trials aiming to demonstrate breakthrough activity of a single-agent anticancer therapy." In the 1970s, the USA FDA usually approved medicines on the basis of ORR (Pazdur, 2008). In the 1980s, it was determined that authorisations for

medicines indicated for cancer should be based on more direct evidence of clinical benefit, such as improvements in overall survival (OS), disease-related symptoms, or physical function (Pazdur, 2008). However, due to an improved understanding of the genomics of cancer, better molecular characterisation of tumours, and more targeted therapies, exceptional rates of response have completely altered the therapeutic background in a number of malignant cancers. The ORR and duration of response, as assessed in single-arm trials, has served as the basis of accelerated approval, and at times regular approval in a number of cancers.

The data achieved in this study was also in line with the data compiled by EMA and published following the 10-year report on its experience with CMAs, with data collected between July 2006 and June 2016.[56]

Marketing authorisation granted under exceptional circumstances is based on less comprehensive data which the applicant is unable to provide over time due to the rarity of the disease, the present state of scientific knowledge and/or ethical constraints. From the data obtained on the licensing status upon initial application of marketing authorisations under exceptional circumstances, 8 medicines were already authorised in the USA, whereas another 8 medicines were already authorised in the EU for another indication. This shows an increasing interest in establishing new medical indications for approved drugs, referred to as drug repositioning, which provides a relatively low-cost and high-efficiency approach for drug discovery (Drent et al, 2016; Liu et al, 2016).

[56] European Medicines Agency (EMA). 10-year report on its experience with conditional marketing authorisations, with data collected between July 2006 and June 2016 [Online]. UK: EMA; 2017 [cited 2017 May 05]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf

Arguably, there have been missed opportunities to expedite approval of several medicines of high value that obtained regular authorisation in the EU, with significant delays compared to their availability in the USA (Roberts et al, 2011; Martinalbo et al, 2016). Global marketing authorisation is now current practice for both large and small pharmaceutical companies. Pharmaceutical companies increasingly have to meet requirements of the EMA, FDA and PMDA. There are differences in marketing authorisation decisions between regulatory agencies, as was demonstrated in the analysis of EMA and FDA approval decisions on anticancer drugs (Trotta et al, 2011; Putzeist, 2013; Makuch and Shi, 2014). On September 17, 2004, the EMA and the FDA agreed to undertake a pilot programme to provide parallel scientific advice (PSA). Since initiation of the pilot programme on January 1, 2005, PSA activities have significantly increased. This increase in PSA activities led to an indefinite extension of the PSA programme on March 13, 2006.[57] Although scientific information between the two agencies is exchanged, independent advice is given to the applicant by both agencies.[58] It would be worth exploring differences in marketing authorisation decisions and the possibility to harmonise marketing authorisation decisions for joint decisions by registration authorities.

When compared to the CMAs, 40% (18 out of 45) of the pivotal studies used for exceptional marketing authorisations were phase II and 31% (14 out of 45) were phase III studies. No phase details were defined for 29% (13 out of 45) of the pivotal studies. Inclusion of data of the non-defined studies could increase the number of completed

[57] United States Food and Drug Administration (FDA). SOPP 8001.6: Procedures for Parallel Scientific Advice with European Medicines Agency (EMA) [Online]. US: FDA; 2013. [cited 2017 May 05]. Available from: https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm061218.htm

[58] European Medicines Agency (EMA). General principles: EMA-FDA parallel scientific advice. EMEA/24517/2009 [Online]. UK: EMA; 2009 [cited 2017 May 05]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf

phase II or phase III studies at application stage for exceptional marketing authorisations.

The pivotal studies used for exceptional authorisations were open-label (58% - 26 out of 45), randomised (47% - 21 out of 45) studies, measuring a change in baseline (25% - 16 out of 63), ORR (20% - 13 out of 63) and immunogenicity (14% - 9 out of 63) as primary efficacy endpoints. Applicants were also successful in using more multiple-arm trials (67% - 30 out of 45) rather than single-arm studies. Similarly to CMAs, open-label studies were also more common, used in 58% (26 out of 45) of the pivotal studies.

Differences between the two authorisation routes were observed, where a larger range of clinical endpoints were used for the pivotal studies and no pattern in the use of the endpoints in the relevant therapeutic areas was observed. Unlike the pivotal studies of the CMAs, 14 pivotal studies (31%) used for exceptional marketing authorisation had multiple primary endpoints. Multiple endpoints may be required when determining that the medicine exhibits a clinical benefit which depends on more than one disease characteristic or outcome being affected. Multiple endpoints may also be used when (1) there are several important aspects of a disease or several ways to assess an important aspect, (2) there is no consensus about which one will best serve the study purposes, and (3) an effect on any one will be sufficient as evidence of effectiveness to support authorisation.

In some cases, multiple aspects of a disease may appropriately be combined into a single endpoint, and subsequent analysis of the components is generally important for

an adequate understanding of the drug's effect.[59] Multiple endpoints could be useful in the study designs of exceptional marketing authorisations due to limited sample size and scientific knowledge of the disease or condition.

The aim of specific obligations for CMAs is to confirm that the benefit/risk balance is positive and to resolve any questions relating to the quality, safety and efficacy of the product, since the authorisation is not intended to remain conditional indefinitely. Specific obligations given for exceptional marketing authorisation provide information on the safe and effective use of the product following authorisation, notwithstanding that provision of this information does not lead to completion of a full dossier.

A limited number of specific obligations required major changes to their scope (3% for CMAs and 6% of exceptional marketing authorisations), indicating that the initially requested type and amount of data to be generated post-authorisation as part of specific obligations are generally maintained. Compliance in terms of study conduct can be considered generally acceptable, since new studies were only imposed rarely based on new results and not driven by non-compliance. Overall, modifications of agreed specific obligations and compliance can be considered acceptable.

In terms of time of completion, a 62% (16 out of 26) of changes for exceptional marketing authorisations were 'due dates for completion'. Minor changes in the 'due dates for completion' are irrelevant but in 10 specific obligations, changes range from 2 to 5 years (n=7) or > 5 years (n=3). Does this imply that there should be a re-

[59] United States Food and Drug Administration (FDA). Multiple Endpoints in Clinical Trials - Guidance for Industry [Online]. US:FDA; 2017 [cited 2017 May 05]. Available from URL: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf

consideration in timelines given for the specific obligations? Should the regulator enforce timelines of the specific obligations given at authorisation?

Although such changes can be driven by difficulties in the conduct of the study, in some cases studies imposed were required to re-substantiate the expected results and in all cases formal extensions were validated with a justification supported by the CHMP. In addition, extensions of due date post-authorisation could reflect a methodical approach by the CHMP at the time of initial authorisation, agreeing only to strict timelines initially and allowing more flexibility only if the applicants present an appropriate justification. Although uncertainties related to data not yet available should be limited in time, an earlier authorisation further impacts public health and patient benefits resulting from earlier access in cases when the positive benefit/risk balance is eventually confirmed.

To support development and availability of high-quality, effective and safe medicines for the benefit of patients, EMA has been offering scientific advice to pharmaceutical developers since 1996. Request for scientific advice by pharmaceutical developers is not mandatory and the scientific advice is not legally binding with regards to the submitted application for the medicine concerned. Scientific advice can be requested during all stages of drug development, including quality and non-clinical and/or clinical issues, and at any stage of the application process, including prior to initial submission, during the assessment procedure and post-authorisation (Regnstrom et al, 2009).

When reviewing the use of scientific advice for conditional and exceptional marketing authorisations, it was noted that 63% (22 out of 35) and 40% (12 out of 30) of

marketing authorisations respectively, have used scientific advice or protocol assistance before or during the review process. For diseases where clinical development is a major challenge, regulatory scientific advice seems a useful tool and should be strongly encouraged. In 2009, Regnstrom et al demonstrated that compliance with scientific advice is associated with a higher rate of successful marketing authorisation.

The number of therapeutic areas where products have managed to obtain CMAs appears limited when compared to marketing authorisations granted under exceptional circumstances. Scientific advice could be a successful tool to explore whether the CMA can be used in other therapeutic areas with seriously debilitating and life-threatening conditions, ensuring timely access to medicines in areas of unmet medical need.

Earlier consideration of the use of conditional or exceptional authorisation led to lesser duration assessment times (Figure 3.4). Improved early dialogue and potential consideration of conditional and exceptional marketing authorisations could support timely assessment of such applications. Use of scientific advice is important in post-authorisation stages to ensure that imposed specific obligations were planned carefully, facilitating completion of additional studies which lead to availability of comprehensive data requested.

Since 2008, EMA has been involving other stakeholders in this process, such as the HTA-bodies to allow pharmaceutical developers to gain simultaneous feedback from both regulators and HTA-bodies, at any point in the developmental lifecycle of medicines. Authorisation of medicines does not necessarily mean that patients have access to the medicines they need and the interaction between EMA and HTA-bodies

can help to establish the evidence required by both parties to determine a medicine's benefit-risk balance and value as efficiently as possible.[53]

This study identified that the European regulatory system has evolved through the years with several initiatives launched to address timely access of innovative medicines to patients including areas of unmet need. Regulation is not the only player to provide access of medicines to patients. Authorised medicines have to be placed on the market at affordable price. Article 35 of the Charter of Fundamental Rights on 'Health protection' provides that "everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices".[60] Article 35 also provides that a high level of human health protection must be ensured in the definition and implementation of all EU policies and activities.

The therapeutic coverage of CAPs including innovative medicines in Malta, results show an imperative public health need, and appropriate actions should be taken to improve and increase access of CAPs in Malta. The analysis showed that 322 ATC codes are not being provided in Malta through the Maltese NHS. This translates to 61% of active substances of CAPs which are not available in Malta. The diseases for which treatments are not available can lead to unacceptable public health burden and imperative medical requirements. Patients in Maltaare being deprived of innovative

[53] United States Food and Drug Administration (FDA). SOPP 8001.6: Procedures for Parallel Scientific Advice with European Medicines Agency (EMA) [Online]. US: FDA; 2013. [cited 2017 May 05]. Available from: https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm061218.htm

[60] European Commission (EC). Charter of fundamental rights of the European Union (2012/C 326/02) [Online]. Official Journal of the European Union 2012; C326:391-407 [cited 2017 May 05]. Available from URL: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012P/TXT&from=EN

solutions for their disease or condition through the NHS and some innovative medicines are only available to the few who can afford to buy them from the private market.

Through discussions with the MMA, DPA and CPSU, the major challenge that was identified as a potential cause of the lack of accessibility of innovative medicines is that Malta is a small member state. This implies that it is a small market where industry may not be interested due to the low, or none at all, profit gained. The geographical position of Malta may be a factor contributing to high prices, since transportation of small quantities of medicines required would further increase the total price. Initiatives were taken and are being taken since this is an evolving cycle of health systems.

Finding a balance between reward for innovation, improved patient access to innovative medicines and controlling budgets is a challenge for decision-makers, patients and industry in all of Europe. The underlying problem could be that the European health care debate focuses too much on regarding innovation as a cost factor. Medical progress perceived as a burden rather than an asset, and the concern is often about the high cost of new medicines rather than on the burden of disease (Cueni, 2008). EU health systems are facing new challenges, including an ageing population, an increasing number of patients affected by chronic diseases and the economic crisis, which has limited the financial resources available. In light of this, European health systems need to be resilient ensuring their sustainability.[61]

[61] Karen Kadenbach. Innovative medicines can maximise health in the EU. The Parliament Politics, Policy and People Magazine [Online]. London; 2016 [cited on 2017 May 05]. Available from URL: https://www.theparliamentmagazine.eu/articles/opinion/innovative-medicines-can-maximise-health-eu

Possible solutions to improve the situation of availability of CAPs in Malta were sought through investigation of alternative use of existing legislative tools to import CAPS in Malta. Legislative tools such as use on a named-patient basis and approval for use in exceptional circumstances are important, and can be a useful way to provide medicines to patients in need when accessibility problems arise.

Parallel distribution for CAPs was never used in Malta before this study and the reasons for this were explored. Since EMA fees was indicated by stakeholders to be the primary cause, analysis of the availability of CAPs through the Maltese NHS was presented to the EMA with a proposal for reduction in notification fees in line with the Maltese fee for parallel importation, that is, reduction from €3,020 to €450. A one-year pilot project with fee reductions for CAPs in the Maltese language was launched in 2016. The obligation for use in the Maltese language was requested to ensure that the medicines were intended to be placed only on the Maltese market. This initiative has led to 5 notification applications for the Maltese market targeting different therapeutic areas, including vaccines and oncology. The impact of this initiative was positive since Maltese patients have benefitted from this initiative by receiving the required treatment.

Since Malta accepts outer medicinal packs in the English language, a number of products are shared packs with the UK and/or Ireland. As indicated in the parallel distribution database compiled by EMA,[49] Malta was already included as a member state of destination together with UK and/or Ireland. This was not known by Maltese wholesalers and awareness on the parallel distribution was launched by the MMA. The

[49] European Medicines Agency (EMA). Parallel distribution [Online]. UK: EMA; 2016 [cited 2017 May 05]. Available from: URL: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000067.jsp&mid=WC0b01ac0580024594

awareness of approved parallel distribution notifications for Malta had a positive impact on the accessibility of CAPs since 7 medicines were imported through parallel distribution in the English language with a reduction in price from the pack imported directly from the MAH. These products were available on the Maltese private market and the reduction in prices can help to make high-priced medicines more affordable for patients if not provided through the Maltese NHS. Reduction in prices can also lead to less expenditure for the Government for these medicines which can result in inclusion of further medicines in the GFL.

Parallel trading is the diversion from the official distribution chain to another distribution chain in another European member state, where it competes with the official distribution chain as a parallel distributor (Costa-Font, 2016). A member state can take advantage of the supply available in another member state to resove accessibility issues. However, parallel trading can indirectly lead to shortages. When the parallel distribution pilot initiative was discussed during the HMA meeting held in Malta in February 2017 and represented by the Heads of all EU member states, the pilot initiative was not seen as creating disadvantages for some member states. On the other hand, interest to extend the initiative to other member states that are facing similar challenges was shown. Further interest by stakeholders including CPSU has been shown for parallel distribution with fee reductions and a proposal was submitted to EMA for extension of the pilot project for CAPs in the Maltese language.

Considerable efforts should be continually exerted for development of viable and effective approaches to balance timely access to innovative pharmaceuticals and sustainability of healthcare systems. From discussions with the DPA and CPSU,

common challenges presented were the limited availability of data, together with data sharing between institutions on the use of innovative medicines.

Implementation of registries within the Maltese NHS should be the next milestone and registries are useful for both regulatory and health technology assessment purposes. The objective of the MMA, DPA and CPSU is oriented towards the entire life cycle of a pharmaceutical product; from pre-authorisation to registration, post-marketing surveillance and pharmacovigilance activity, inspection and certification, economic strategy and pharmaceutical policy, including pricing and procurement of medicines, monitoring and governance of public pharmaceutical expenditure, and post-marketing assessment and health-technology assessments.[33,34]

Robust models of registries monitoring systems have been implemented in several member states, one of which is the monitoring registries system of the Italian medicines agency. This model has been operational in Italy since 2005, primarily to improve early access to innovative therapies, guarantee sustainability and affordability of treatments, collect epidemiological data and monitor the appropriate usage of several treatments. Monitoring registries enable standardised procedures for computerised management of each treatment phase, including patient eligibility, supply, dispensing, follow-up, and allow analysis of consumption data, together with payback or other financial mechanisms (Palazzo et al, 2012; Montilla et al, 2015).

[33] Malta Medicines Authority (MMA). Malta Medicines Authority website [Online]. Malta: MMA; 2017 [cited 2017 May 05] Available from: URL: http://www.medicinesauthority.gov.mt/home?l=1

[34] Ministry for Health. Ministry for Health website [Online]. Malta: Ministry for Health; 2017 [cited 2017 May 05]. Available from: URL: http://health.gov.mt/en/Pages/health.aspx

Set up and monitoring of registries could potentially be linked to other available healthcare databases, through general demographic information, respecting privacy and protecting personal data. For each medicine included in the registry, access is normally dependent on the issue of a prescription by the consultant, following registration and upload of clinical data of the eligible patient. The prescriber should fill in a patient-based electronic request for each dose of treatment administration. This request is automatically submitted by electronic mail to the hospital or community pharmacy, which will be dispensing the requested medicine. The fully automated workflow allows the prescriber to track and monitor several parameters such as therapeutic drug indication, patient benefit in comparison to data collected by trials, potential risk of adverse events, drug interactions and therapy cost. The system also checks eligibility criteria for correct use (Montilla et al, 2015).

The role of e-health is becoming increasingly important, and further investment is planned so as to make more use of e-health services in the Maltese health system, in particular from the European Regional Development Fund.[62] In line with the National Health Systems Strategy for 2014–2020,[63] investment in e-health will enable the electronic patient records in the primary health care sector, electronic prescriptions, entitlement approval system, health data exchange, fully digitised patient registries and improved national electronic health records. This will be a positive milestone for patients and for sustainability of the healthcare system (Azzopardi-Muscat et al, 2017).

[62] European Commission (EC). European Regional Development Fund [Online]. Brussels: EC; 2017 [cited 2017 May 05]. Available from URL: http://ec.europa.eu/regional_policy/en/funding/erdf/

[63] Parliamentary Secretariat for Health, Ministry for Energy and Health (MEH). A national health system strategy for Malta 2014-2020 – Securing our health systems for future generations [Online]. Valletta: MEH; 2017 [cited 2017 May 05]. Available from URL: https://health.gov.mt/en/CMO/Documents/alert_nhss_eng.pdf

New scientific progress in innovative medicines and improved diagnosis of diseases are leading regulators and payers to focus their attention towards real life settings. To date, Malta has not engaged in any managed entry agreements with other member states for procurement of innovative medicines. Although regulators and payers are taking into consideration patient pressures for rapid access to treatment, nevertheless regulators and payers must balance the difficulties of taking significant decisions with uncertainties when deciding on pricing and reimbursement processes (Muscolo et al, 2014).

Following the EMA proposal for adaptive licensing, an instrument to balance early access to innovative medicines to patients with the need of collecting information on the medicines' benefits and risks, the Maltese NHS has to prepare itself towards direction of innovative pay per performance models.

Evidence from Europe points to a significant uptake of managed entry agreements over the past few years and suggests that over 75% of all managed entry agreements aim to address budget impact, either alone or in combination with cost-effectiveness, use or both. The most common features of managed entry agreements are price volume agreements, followed by requirements for data collection, and limited access to eligible patients (Ferrario and Kanavos, 2013).

Endeavouring in managed entry agreements can potentially convey benefits, such as faster access to innovative medicines, coverage, and a tool to deal with uncertainty. Several challenges need to be overcome, including the current general lack of transparency and evidence surrounding these schemes, need for good information systems together with the ability to monitor outcome and use, and development of clear

and objective decision-making criteria to guide data collection, evaluation and the final reimbursement decision (Kanavos et al, 2017).

Compassionate use refers to a manufacturer providing a therapeutic product, often without charge, to patients in need of a medicine, on a temporary basis. Malta is also benefitting from this initiative to increase access to innovative medicines at no cost. A compassionate use programme is different from a clinical trial and, strictly, cannot be used for investigational purposes or commercial pre-authorisation activities. Promotion of the medicinal products under a compassionate use programme or the programme itself is not permitted (Sou, 2010).

Since not all companies contribute to compassionate use programmes, one may question the reason for a profit-making company or organisation donating a medicine. For commercial reasons a company may prefer to donate a medicine rather than sell at a discounted rate to member states (Roos et al, 2010). Discounted prices could prompt requests from other member states to reduce the cost of the medicine. A company would then rather donate the medicines for compassionate use rather than offer the discounted price to all patients in the EU, and with significant effects on the profits. Donating the medicine would avoid downward harmonisation of the price.

Increasing experience with the use of compassionate use programmes in Malta may be a tool to improve accessibility of innovative medicines and can also provide invaluable clinical data particularly in rare diseases investigated in clinical trials which often embrace relatively few patients. Clinical data obtained from compassionate use provides further ‘real world’ data about responses in patients who may not meet the inclusion

criteria for clinical trials. Phase III clinical trials in this field are designed principally to investigate efficacy using protocols that regulators approve, and often exclude patients with advanced disease or co-morbidities. All EU countries, including Malta, should maintain registers of adverse events occurring during compassionate use programmes, to support identification of adverse events and interactions with other medicines at an early stage, and thereby contributing to the safety profile of the medicines leading to refining of indications, dosage, interactions and special precautions during use (Hyry et al, 2015).

4.2 Study limitations

During analysis of the conditional and exceptional marketing authorisations, the main limitation was that the total number (65) of successful marketing authorisations has limited opportunities for analysis. The required data for this analysis was extracted from the EPARs and these were the only data source used. Despite that EPARs are standardised documents in terms of structure and subheadings, EPARs differed in length, completeness and amount of detail. This was mostly seen in the EPARs for exceptional marketing authorisations approved prior to 2006. Heterogeneity in the content of EPARs might have introduced some misclassification.

Analysis of the impact of accessibility of CAPs was carried out by using the CAPs provided by the Maltese NHS and did not consider CAPs which can be accessed through the private market. Due to the high-cost of CAPs, it was assumed that only a few patients can afford to buy these medicines from the private market on a long-term basis.

4.3 Recommendations for further research

This study focused on two early regulatory access tools which were the conditional and exceptional marketing authorisations. Only successful conditional and exceptional marketing authorisations were considered in this study. Further analysis on the scientific grounds for unsuccessful conditional and exceptional marketing authorisations could provide further data for both the industry and regulators. In addition, rather than looking into all active substances authorised through the conditional and exceptional route from 2001-2016 as outlined in this study, analysis can also be carried out for active substances according to therapeutic areas, such as oncology and infectious diseases.

Further research can be carried out on other early access tools, such as use of accelerated assessments in the EU and use of compassionate programmes in the EU including Malta. Studies on the implementation of innovative methodologies and systems by the Maltese NHS such as setting up of a robust model for registriescan be carried out to ensure that the Maltese NHS is a competent player in the EU network with regards to the. The impact of the accessibility of innovative medicines can also be studied at from the private market perspective and from exceptional approvals granted to specific patients for innovative medicines not available through the Maltese NHS.

4.4 Conclusions and study contributions

This study confirmed an increase in the number of innovative medicines authorised for today's EU markets since the inception of the centralised procedure and launch of early access pathways and initiatives. The success of this regulation is attributed to the number of medicines targeting unmet medical needs, and in the promotion of public awareness and patient involvement in the treatment of these rare, and in some cases life-threatening, diseases.

Despite of this groundbreaking progress in the management, diagnosis, and treatment of diseases, limitations have made it difficult to make therapeutically important medicines available at an earlier time. To overcome this issue, EMA has introduced authorisation flexibilities, such as the conditional and exceptional marketing authorisations, to ensure that patients have earlier access to treatments for rare disease conditions with no alternative treatment available.

During the review of the EU Directives, regulations and guidelines, a glossary including 270 regulatory terms was compiled and validated for use in the pharmaceutical and academic setting.

To-date, 35 innovative medicines were granted a CMA and 30 innovative medicines have been granted authorisation under exceptional circumstances. Twenty-eight of the conditional or exceptionally authorised products were given a new active substance status and 33 were given orphan designation. Innovative medicines have shown evidence of therapeutic innovation and met accepted standards of safety and efficacy during CHMP assessment before being made available to patients. Following

authorisation, five products were withdrawn due to commercial reasons, one product was withdrawn for lack of efficacy and one product was withdrawn for lack of requested additional data.

Key determinants of authorisations were analysed, including study designs of the main and pivotal clinical studies. Use of phase II/III, randomised, open-label studies with appropriate use of clinical endpoints were highlighted for all conditional and exceptional marketing authorisations. Current and potential use of tools, such as scientific advice provided by expert committees of EMA were identified to assist industry in appropriate selection of study designs prior to initial application which could lead to shorter assessment times and earlier market access.

Accessibility of innovative medicines authorised through the centralised procedure was confirmed to be limited in Malta. This study showed that in 2015, when a total of 822 CAPs covering 522 ATC Codes were authorised, the Maltese NHS did not include 322 (61%) CAP ATC codes. Challenges were discussed with the MMA, DPA and CPSU and prospective solutions for the future sustainability of the Maltese NHS were identified. The move towards collection of real-world data in innovative areas where uncertainties of relative effectiveness and safety persist, was highlighted through the use of compassionate programmes and managed entry agreements in collaboration with other member states.

Existing legislative and regulatory tools were explored and their potential use in improving accessibility was assessed. Approvals on a named patient basis or approvals in exceptional cases are being used to provide patients with the required innovative

treatment when decision is being taken on an individual patient level. Parallel distribution was an unexplored tool in Malta, where no CAP was imported through parallel distribution. The parallel distribution pilot project launched by the EMA specifically for the Maltese market was a target regulatory initiative instigated through this study to help overcome accessibility barriers, which was beneficial to increase accessibility of medicines in practice. This study is being used as an example by the European Commission to show that, in the interest of European citizens, flexibility in the regulation is possible, confirming an innovative concept of changing the perception of the EU that regulations are not biased towards safety and efficacy at the detriment of accessibility.

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APPENDIX 1

Glossary

A

Abuse

Sporadic or persistent, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (European Medicines Agency and Heads of Medicines Agencies, 2014a).

Accelerated assessment

Rapid assessment of medicines in the centralised procedure of major interest for public health, especially therapeutic innovations. Accelerated assessment usually takes 150 evaluation days, rather than 210 days (European Commission, 2004b).

Access to healthcare

Timely use of personal health services to achieve the best health outcomes (Institute of Medicine, 1993).

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (International Conference on Harmonisation, 2000).

Active substance

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action to restore, correct or modify physiological functions or to make a medical diagnosis (European Commission, 2001b).

Active substance intermediate

A substance obtained during the production of an active substance and which is intended for further processing (European Commission, 2014b).

Active Substance Master File (ASMF)

Documentation providing detailed information on the manufacturing of the active substance of a medicine (European Medicines Agency, 2017a).

Active substance starting material

Any substance from which an active substance is manufactured or extracted (European Commission, 2014b).

Adaptive pathways

Scientific concept of medicines development and data generation for medicines in areas of high medical need where collection of data via traditional routes is difficult and with potential for a gradual extension of the target population and possibility to collect and use real-world data (European Medicines Agency, 2017a).

Advanced therapy medicinal product (ATMP)

A medicinal product for human use that is either a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered product (European Commission, 2007).

Adverse drug reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological function (European Medicines Agency and Heads of Medicines Agencies, 2014b).

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (European Medicines Agency and Heads of Medicines Agencies, 2014).

Anatomical Therapeutic Chemical (ATC) system

A classification system used to classify the captured indications. The ATC system is a pharmaceutical coding system that divides drugs into different groups according to the organ or system on which they act and the therapeutic and chemical characteristics (WHO Collaborating Centre for Drug Statistics, 2011).

Annual reassessment

An annual review of the benefits and risks of a medicine that has been authorised under exceptional circumstances. As part of the process, the specific obligations imposed on the marketing-authorisation holder are also reviewed (European Commission, 2001b; European Commission, 2004b; European Medicines Agency, 2017a).

Anti-tampering device

Safety feature allowing verification of whether the packaging of a medicinal product has been tampered with (European Commission, 2016).

Applicant

Person or company that applies for registration, licensing or marketing authorisation of a new pharmaceutical product or an update or variation to an existing marketing authorisation (International Conference on Harmonisation, 2007a).

Article-58 application

An application for a scientific opinion on the use of a human medicine intended exclusively for markets outside the European Union. Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest (European Medicines Agency, 2017a).

Assessment Report (AR)

Documents explaining why a marketing authorisation and each of the proposed indications have been or can be approved or rejected by the reference member state in mutual recognition and decentralised procedures and Committee for Medicinal Products for Human Use (CHMP) in centralised procedures and details the benefit-risk assessment for the product. It also serves as an audit trail explaining why an authorisation has been proposed, granted, or rejected and explaining the terms of the summary of product characteristics (SmPC), package leaflet (PL) and label (Coordination Group of Mutual Recognition and Decentralised Procedures - Human, 2017; European Medicines Agency, 2017b).

Audit

A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (European Committee for Standardisation, 2015).

Audit finding

Results of the evaluation of the collected audit evidence against audit criteria (European Committee for Standardisation, 2015).

Audit plan

Description of activities and arrangement for an individual audit (European Committee for Standardisation, 2015).

Audit programme

Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (European Committee for Standardisation, 2015).

B

Batch

A defined quantity of starting material, packaging material or bulk, intermediate or finished product intended or purported to be homogeneous in character and quality, and which has been produced during a defined cycle of manufacture (International Conference on Harmonisation, 2007a).

Batch certificate

A document which provides information on quality of a particular batch (International Conference on Harmonisation, 2007a).

Batch manufacturing record

A document stating the materials used and operations carried out during the processing of a given batch, including details of in-process controls and packaging information (International Conference on Harmonisation, 2007a).

Batch number

A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and permits its history to be traced (International Conference on Harmonisation, 2007a).

Batch recall

The action of withdrawing a batch from the distribution chain and users. A batch recall may be partial, in that the batch is only withdrawn from selected distributors or users (European Commission and European Medicines Agency, 2014b).

Benchmarking of European Medicines Agencies (BEMA)

Benchmarking programme among the human and veterinary medicines agencies. The programme aims to contribute to the development of a world-class medicines regulatory system based on a network of agencies operating to best practice standards. BEMA is based on assessment of the systems and processes in individual agencies against a set of indicators which have been agreed in the following areas: Management systems; Assessment of marketing authorisation applications; Pharmacovigilance activities; and Inspection services (Heads of Medicines Agencies, 2017a).

Bioavailability

Measurement of the rate and extent to which a drug reaches the site of action (Shargel and Yu, 1999).

Bioequivalence

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy (Committee for Human Medicinal Products, 2010).

Biological medicine

A medicine whose active substance is made by a living organism (European Medicines Agency, 2017a).

Biomarker

Tests that can be used to follow body processes and diseases in humans and animals. Biomarkers can be used to predict how a patient will respond to a medicine or whether they have, or are likely to develop, a certain disease (European Medicines Agency, 2017c).

Biosimilar

A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EU/EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy

based on a comprehensive comparability exercise needs to be established (Committee for Human Medicinal Products, 2014).

Blinding

The deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor (European Commission, 2003b).

Brokering of medicinal products

All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person (European Commission, 2001b).

C

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements (International Conference on Harmonisation, 2000).

Centralised procedure (CP)

A European Community registration procedure for the authorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the European Community. This procedure is compulsory for medicinal products derived from biotechnology and for those in four specific therapeutic areas (products against HIV, cancer, neurodegenerative diseases and diabetes), and is available at the request of companies for other innovative new products (European Commission, 2004b).

Certificate of Analysis (CoA)

A documented testimony issued by an authorised person showing conformity or non-conformity to the specifications (International Conference on Harmonisation, 2007a).

Certificate of Suitability (CEP)

Document providing proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia by means of a certificate of suitability granted by the Certification Secretariat of the European Directorate for the Quality of Medicines (European Commission, 2003a).

Chemistry, Manufacturing and Control (CMC)

Information on the chemistry, manufacturing and controls to be submitted for drug substances and drug products to ensure continued product quality. The guidances are related to Module 3, Quality, of the Common Technical Document (International Conference on Harmonisation, 2003).

Clinical trial endpoint

A measure that allows investigators to decide whether the null hypothesis of a clinical trial should be accepted or rejected (Bakhai et al, 2006).

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy (European Commission, 2001a).

Clinical Trial Facilitation Group (CTFG)

Facilitation group of the Heads of Medicines Agencies network to coordinate the implementation of the EU clinical trials directive 2001/20 EC across the member states. In relation to clinical trials the CTFG

acts as a forum for discussion to agree on common principles and processes to be applied throughout the European medicines regulatory network. It also promotes harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities (Heads of Medicines Agencies, 2017b).

Clock stop

A period of time during which the evaluation of a medicine is officially stopped, while the applicant prepares responses to questions from the regulatory authority. The clock resumes when the applicant has sent its responses (European Medicines Agency, 2017a).

Committee for Advanced Therapies (CAT)

Committee responsible for the assessment of the quality, safety and efficacy of advanced-therapy medicines, including medicines classified as gene therapy, somatic-cell therapy or tissue-engineered products (European Commission, 2007).

Committee for Medicinal Products for Human Use (CHMP)

Committee responsible for preparing the European Medicines Agency's opinions on all questions concerning medicinal products for human use (European Commission, 2004b).

Committee for Orphan Medicinal Products (COMP)

Committee responsible for examining any application for the designation of a medicinal product as an orphan medicinal product (European Commission, 2000).

Committee on Herbal Medicinal Products (HMPC)

Committee responsible for establishing Community herbal monographs and preparing the European Medicines Agency's opinions on questions relating to herbal medicines (European Commission, 2004a).

Common European Submission Portal (CESP)

A system which provides a simple and secure mechanism for exchange of information between applicants and regulatory agencies. The purpose of the system is to: (1) Provide a secure method of communicating with the regulatory agencies via one platform; (2) Allow submission of an application once to reach all required regulatory agencies; (3) Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD (Heads of Medicines Agencies, 2015).

Common Technical Document (CTD)

Set of specifications for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. It was developed by the European Medicines Agency (EMA, Europe), Food and Drug Administration (FDA, US) and Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (International Conference on Harmonisation, 2016a).

Communication and Tracking System (CTS)

A system used by the National Competent Authorities (NCAs) involved in the licensing of human and veterinary medicinal products via the mutual recognition and decentralised procedures. CTS supports the co-ordination and tracking of marketing authorisation, post licensing and work sharing procedures (European Medicines Agency, 2011).

Compassionate Use

Use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions. This helps to make medicines that are still under development available to patients (European Commission, 2004b).

Competent Authority

An organisation responsible for the authorisation and supervision of medicinal products (European Commission, 2004c).

Compilation of Community Procedures

A collection of GMP inspection-related procedures and forms agreed by the GMP inspectorates of all the Member States and are designed to facilitate administrative collaboration, harmonisation of inspections and exchange of inspection-related information (European Commission, 2004c).

Concerned Member State (CMS)

A member state that is concerned with an application for mutual recognition or decentralised, and expected to recognise the initial approval of the Reference Member State (RMS) (European Medicines Agency, 2017b).

Conditional Marketing Authorisation (CMA)

Approval of a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future (European Commission, 2006a).

Contraindication

Situation in which the drug should not be used because of the risk of use which outweighs any possible beneficial effects (International Conference on Harmonisation, 2007a).

Co-ordination Group for Mutual Recognition and Decentralised procedures (human) (CMDh)

A group of the Heads of Medicines Agencies responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure (Heads of Medicines Agencies, 2017c).

Co-Rapporteur

One of the two members of a committee or working party leading the assessment of an application (European Commission, 2004b).

Council for International Organizations of Medical Sciences (CIOMS)

A not-for-profit international non-governmental organization established jointly by the World Health Organisation (WHO) and United Nations Educational, Scientific and Cultural Organisation (UNESCO). The organisation brings together representatives from the "biomedical scientific community" worldwide, aiming to encourage and facilitate international biomedical scientific activities whilst maintaining a relationship with the United Nations organisation (Council for International Organizations of Medical Sciences, 2017).

Counterfeit medicine

Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used. (European Commission, 2011).

Crisis

A situation where, after assessment of the associated risks, urgent and coordinated action within the EU regulatory network is required to manage and control the situation (European Medicines Agency, 2014).

D

Data exclusivity

Period of eight years from the initial authorisation of a medicine during which the marketing-authorisation holder benefits from the exclusive rights to the results of preclinical tests and clinical trials on the medicine. After this period, the marketing authorisation holder is obliged to release this information to companies wishing to develop generic versions of the medicine (European Commission, 2015).

Decentralised procedure (DCP)

Orocedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State (European Commission, 2015).

Declaration of interest (DoI)

Provision of information on all potential conflicts of interests by an individual, including recent work activities, investments and family connections with the pharmaceutical industry (European Commission, 2004b).

Deferral (Paediatric)

Possibility to defer a measure in a paediatric investigation plan until after studies in adults have been conducted. This ensures that research in children is done only when it is safe and ethical to do so. (European Commission, 2014).

Detailed Description of the Pharmacovigilance System (DDPS)

A detailed description of the pharmacovigilance system which enables the collection, monitoring, assessment and evaluation of information related to adverse events, submitted as part of a Marketing Authorisation Application (European Medicines Agency, 2012).

Deviation

Non-fulfilment of a requirement (European Committee for Standardisation, 2015).

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 and Heads of Medicines Agencies, 2012).

Dosage form

The form of the completed pharmaceutical product, e.g. tablet, capsule, injection, elixir, suppository (European Commission, 2004c).

Drug interaction

An act of two or more drugs affecting each other pharmacodynamically and pharmacokinetically (International Conference on Harmonisation 2007a).

Drug Master File (DMF)

Documentation providing detailed information on the manufacturing of the active substance of a medicine. Also known as active substance master file. (European Medicines Agency, 2017a).

E

Efficacy

Ability of a drug or treatment to produce a specific result, regardless of dosage (Pitler and White, 1999).

Electronic Common Technical Document (eCTD)

An interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission (European Medicines Agency, 2017d).

eSubmission Gateway

Electronic submission channels of the European Medicines Agency gateway that allow the applicants to submit documents supporting all types of applications for human medicines to the Agency securely over the internet in the Electronic Common Technical Document (eCTD) format (European Medicines Agency, 2017d).

EudraCT

EU system for the registration of clinical trials (European Medicines Agency, 2011).

EudraGMP

Database to facilitate the exchange of information on compliance with good manufacturing practice (GMP) among the competent regulatory authorities within the European medicines network (European Medicines Agency, 2011).

EudraGMP administrator

An individual within a national competent authority or European Medicines Agency who is responsible for allocating user roles and for the maintenance aspects of the EudraGMDP user group and database (European Commission, 2004c).

EudraLex

Web server for the on-line dissemination of Community guidelines, Notice to Applicants and pharmaceutical legislation (European Commission, 2017a).

EudraLink

A highly secure email system designed by the European Medicines Agency for the transmission of confidential scientific data by both pharmaceutical companies and national competent authorities (European Medicines Agency, 2017b).

EudraNet

A secure network and the backbone of the European Medicines Regulatory System. It facilitates secure communication, and also enables secure access to applications hosted at the European Medicines Agency (European Medicines Agency, 2011).

EudraPharm

A database designed to hold information on each medicinal product (Human and Veterinary use) authorised in the European Union, and the European Economic Area. The system is required to hold the information contained in the Summary of Product Characteristics, the Package Leaflet and the labelling. Its purpose is to provide authoritative information to all stakeholders, including in particular the general public (European Medicines Agency, 2011).

EudraVigilance

EU database on adverse drug reactions that receives, processes and stores individual case safety reports for all medicines authorised in the European Union (European Medicines Agency, 2011).

European Commission (EC)

EU's politically independent executive arm. It is alone responsible for drawing up proposals for new European legislation, and it implements the decisions of the European Parliament and the Council of the EU (European Union, 2017).

European Commission decision

The legally binding decision issued by the European Commission at the end of a regulatory procedure, such as a marketing authorisation application or arbitration procedure. A European Commission decision comes after an opinion from one of the Agency's scientific committees (European Medicines Agency, 2017a).

European Directorate for the Quality of Medicines and Healthcare (EDQM)

A leading organisation that protects public health by enabling the development; supporting the implementation; and monitoring the application of quality standards for safe medicines and their safe use. (European Directorate for the Quality of Medicines and Healthcare, 2017a).

European Drug Regulatory Network (EudraNet)

A private electronic network linking the members of the European medicines regulatory network and the European Medicines Agency (HMA, 2017d).

European Economic Area (EEA)

Consists of the member states: Iceland, Liechtenstein and Norway (European Commission, 2004c).

European Federation of Pharmaceutical Industries Associations (EFPIA)

European association representing the pharmaceutical industry operating in Europe, to promote pharmaceutical discovery and development in Europe and to bring to the market medicinal products in order to improve human health worldwide (European Federation of Pharmaceutical Industries Associations, 2017).

European Free Trade Association (EFTA)

An intergovernmental organisation set up for the promotion of free trade and economic integration to the benefit of its four Member States: Iceland, Liechtenstein, Norway and Switzerland (European Free Trade Association, 2017).

European Medicines Agency (EMA)

A decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU (European Medicines Agency, 2017e).

European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX)

A discussion forum at which representatives exchange views on legal and related issues to reach an insight on the issue and define common principles to be applied throughout the European Medicines Regulatory Network and in dealing with national issues (Heads of Medicines Agencies, 2017e).

European Pharmacopoeia

A major regional pharmacopoeia which provides common quality standards throughout the pharmaceutical industry in Europe to control the quality of medicines, and the substances used to manufacture them (European Directorate for the Quality of Medicines and Healthcare, 2017).

European Pharmacovigilance Issues Tracking Tool (EPITT)

A system that effectively tracks and monitors all Pharmacovigilance Working Party recommendations, summary of product characteristics implementations and all safety issues regardless of the authorising procedure of the product, as many safety issues involve multiple medicinal products across all authorising procedures (European Medicines Agency, 2011).

European Public Assessment Report (EPAR)

Set of documents describing the evaluation of a medicine authorised via the centralised procedure and including the product information, published on the European Medicines Agency website (European Medicines Agency, 2017a).

European Union Review System (EURS)

A system that validates, stores and presents electronically submitted marketing authorisation application dossiers for review, using the functionality of the eCTD to enable information through the lifecycle of the medicinal product to be displayed according to the requirements of the reviewer (European Medicines Agency, 2011).

Eudravigilance Website (EVWEB)

A web interface which provides interactive tools to allow for a 'manual' safety and acknowledgement message, as well as medicinal product report generation and administration by a user via a web interface (European Medicines Agency, 2017f).

Exceptional marketing authorisation

A type of marketing authorisation granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical (European Medicines Agency, 2005).

Excipient

Any constituent of a medicinal product other than the active substance and the packaging material (European Commission, 2001b).

Expiry Date

The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container-closure system (International Conference on Harmonisation, 2007a).

F

Falsified medicinal product

Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used (European Commission, 2011).

Food and Drug Administration (FDA)

In the United States, the FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation (Food and Drug Administration, 2017a).

Freedom of information (FOI)

The right to the general public to information held by public authorities in order to promote added transparency and accountability in government (Bayne, 1984).

G

Generic medicine

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 Commission, 2001b).

Gene-therapy medicine

A biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence (European Commission, 2012).

Genomic Biomarker

A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions (International Conference on Harmonisation, 2007b).

Good Clinical Practice (GCP)

A code of international standards concerning the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. Good clinical practice provides assurance that a study's results are credible and accurate and that the rights and confidentiality of the study subjects are protected (European Medicines Agency, 2017a).

Good Distribution Practice (GDP)

A code of standards ensuring that the quality of a medicine is maintained throughout the distribution network, so that authorised medicines are distributed to retail pharmacists and others selling medicines to the general public without any alteration of their properties (European Medicines Agency, 2017a).

Good Laboratory Practice (GLP)

A code of standards concerning the testing of medicines in laboratories during their development (European Commission 2004c).

Good Manufacturing Practice (GMP)

A code of standards which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use (European Commission, 2003b).

Good Pharmacovigilance Practice (GVP)

A set of measures drawn up to facilitate the performance of the safety monitoring of medicines in the European Union (European Medicines Agency, 2017a).

Good Practice (GxP)

Abbreviation for generic good practice, which refers to the series of laws, regulations, and guidance that govern various areas of the research, development, testing, manufacturing, and distribution of medicines (European Patients' Academy, 2017).

Guideline

A document providing guidance on the scientific or regulatory aspects of the development of medicines and applications for marketing authorisation. Although guidelines are not legally binding, applicants need to provide justification for any deviations (European Medicines Agency, 2017a).

H

Harm

Damage to health including damage that can occur from the loss of product quality or availability (International Conference on Harmonisation, 2005).

Heads of Medicines Agencies (HMA)

A network of the Heads of the National Competent Authorities whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the EU/EEA. The HMA addresses key strategic issues for the network, such as the exchange of information, IT developments and sharing of

best practices; focuses on the development, co-ordination and consistency of the European medicines regulatory system; ensures the most effective and efficient use of resources across the network (Heads of Medicines Agencies, 2017).

Health Technology Assessment (HTA)

A multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value (European Commission, 2017c).

Health Technology Assessment Body (HTA-body)

A public organisation that provides recommendations on the medicines and other healthcare interventions that can be paid for or reimbursed. These organisations look at the relative effectiveness and cost effectiveness of medicines that have been authorised (European Medicines Agency, 2017g).

Healthcare professional

Medically qualified persons, such as physicians, dentists, pharmacists and nurses (European Medicines Agency, 2004).

Homeopathic medicinal product

Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the member states (European Commission, 2001b).

Hybrid medicine

A medicinal product that does not fall within the definition of a generic medicinal product; or where the bioequivalence cannot be demonstrated through bioavailability studies; or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided (European Commission, 2001b).

Immediate packaging

Container or other form of packaging immediately in contact with the medicinal product (European Commission, 2001b).

Immunological medicinal product

Any medicinal product consisting of vaccines, toxins, serums or allergen products (European Commission, 2001b).

Incident

A situation where an event occurs or new information arises, irrespective whether this is in the public domain or not, in relation to (an) authorised medicinal product(s) which could have a serious impact on public health (European Medicines Agency and Heads of Medicines Agencies, 2014b).

Indication

Disease and the population for which the benefit risk balance of the medicine is positive (European Medicines Agency, 2013a).

Individual case safety report (ICSR)

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 and Heads of Medicines Agencies, 2014c).

Inspection

On-Site assessment of the compliance with the Community GMP principles performed by officials of Community Competent Authorities or authorities found equivalent under a Mutual Recognition Agreement (European Commission, 2004c).

Inspection report

Report prepared by the official representing the Competent Authority stating whether the company inspected in general complies with the Community GMP principles and/or the product and process related issues arising from the assessment of the application (European Commission, 2014b).

International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

Council that brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration (International Council on Harmonisation, 2017).

International Non-proprietary Name (INN)

Official non-proprietary or generic name given to a pharmaceutical substance (World Health Organisation, 2017a).

Interventional clinical trial

An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (e.g., preventive care, drugs, surgical procedures, behavioural treatments, etc.) to evaluate their effects on health-related outcomes (European Medicines Agency, 2008).

Investigational medicinal product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (European Commission 2001).

Investigator

A doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator (European Commission 2001).

ISO9000

A series of international standards for quality systems (European Committee for Standardisation, 2015).

J

Joint Audit Programme (JAP)

A programme on the quality system adopted by GMP inspectorates aiming at ensuring consistency of GMP standards and a harmonised approach throughout Europe (European Medicines Agency, 2017h).

L

Labelling

Information on the immediate or outer packaging (European Commission, 2001b).

Licence

A legal document which authorises an individual or any entity to perform a given operation (International Conference on Harmonisation, 2007a).

M

Managed Entry Agreement (MEA)

An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact (Klemp et al, 2011).

Manufacturing

Any total or partial operation of receipt of materials, production, packaging, repackaging, labelling, re-labelling, quality control or release of active substances, and the related controls (European Commission, 2014a).

Market exclusivity

10-year period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market (European Medicines Agency, 2017a).

Marketing Authorisation (MA)

Approval to market a medicine in one, several or all European Union member states (European Commission, 2015).

Marketing Authorisation Application (MAA)

Document used as the basis for a marketing application (an application for approval to market the product based on a full review of all quality, safety, and efficacy data, including clinical study reports) (European Commission, 2001b).

Marketing Authorisation Holder (MAH)

A person who has applied and received right to market and sell a product in a pharmaceutical form or a set of pharmaceutical forms (European Commission, 2004c).

Medication Error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (European Medicines Agency, 2015).

Medical prescription

Any medicinal prescription issued by a professional person qualified to do so (European Commission, 2001b).

Medicinal product

Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product (European Commission 2001b).

Member State (MS)

A country member of the European Union (European Commission, 2004c).

Misuse

Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorised dose, route of administration, and/or the indication(s) or within the legal status of its supply

(e.g. without prescription for medicinal products subjects to medical prescription) (European Medicines Agency and Heads of Medicines Agencies, 2014a).

Mock-up

Copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three-dimensional presentation of the label text is clear (European Medicines Agency, 2017i).

Module I of the Common Technical Document

Administrative Information and Prescribing Module outlining the Summary of the Dossier which includes application forms, summary of Product Characteristics, packaging, Expert Reports (International Conference on Harmonisation, 2016b).

Module II of the Common Technical Document

Common Technical Document Summaries Module outlining a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use (International Conference on Harmonisation, 2016b).

Module III of the Common Technical Document

Module with information on the Quality of the drug substance (International Conference on Harmonisation, 2016b).

Module IV of the Common Technical Document

Module outlining the non-clinical study reports of the drug substance (International Conference on Harmonisation, 2016b).

Module V of the Common Technical Document

Module outlining the clinical study reports of the drug substance (International Conference on Harmonisation, 2016b).

Multi-centre clinical trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries (European Commission 2001).

Mutual Recognition Agreement (MRA)

An agreement between 2 regulatory agencies to recognize the regulatory assessment or inspection of a site or review conducted by one another. MRA countries include Australia, Switzerland, New Zealand, Canada and Japan (European Commission, 2004c).

Mutual recognition procedure (MRP)

A procedure through which an authorisation of a medicine in one European Union Member State is recognised by another Member State (European Commission, 2004c).

N

Name of medicinal product

Name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder (European Commission, 2001b).

National Competent Authority

An organisation in the European Union/European Economic Area responsible for the authorisation and supervision of medicinal products (European Commission, 2004c).

National Marketing Authorisation

Any marketing authorisation granted by a Member State in accordance with the acquis outside the mutual recognition or decentralised procedure and that has not been subject to a complete harmonisation following a referral procedure (European Commission, 2008a).

Non-interventional clinical trial

A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data (European Commission, 2001b).

Notice to Applicants (NtA)

Document prepared by the European Commission in consultation with the competent authorities of the Member States, the European Medicines Agency and interested parties. The NTA is published in the following volumes: Volume 2A dealing with procedures for marketing authorisation; Volume 2B dealing with the presentation and format of the application dossier; and Volume 2C dealing with regulatory guidelines (European Commission, 2008b).

O

Occupational exposure

Exposure to a medicinal product for human use as a result of one's occupation (European Medicines Agency and Heads of Medicines Agencies, 2014b).

Off-label use

Intentional use of a medicinal product for a medical purpose not in accordance with the authorised product information (European Medicines Agency and Heads of Medicines Agencies, 2014a).

Opinion

A scientific conclusion given by the Committee for Human Medicinal products (CHMP) on issues related to medicinal products, such as whether the data submitted allow the conclusion to be drawn that there is an overall positive benefit/risk of a new product in a proposed indication and whether the product should be placed on the market (European Medicines Agency, 2017a).

Organisation

Person or group of people that has its own functions with responsibilities, authorities and relationships to achieve its objectives (European Committee for Standardisation, 2015).

Orphan designation

A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain

criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market (European Commission, 2000).

Orphan Medicinal Product

A medicinal product (a) intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition (European Commission, 2000).

Outer packaging

Packaging into which is placed the immediate packaging (European Commission, 2001b).

Overdose

Administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorised product information. This shall also take into account cumulative effects due to overdose (European Medicines Agency and Heads of Medicines Agencies, 2014a).

P

Packaging

All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product (European Commission, 2004c).

Paediatric Committee (PDCO)

Committee of the European Medicines Agency responsible for assessing the content of paediatric investigation plans, which describe how a medicine should be studied in children, as well as waivers and deferrals (European Commission, 2006b).

Paediatric investigational plan (PIP)

A research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population (European Commission, 2006b).

Paediatric population

Population aged between birth and 18 years (European Commission, 2006b).

Parallel Distribution (PD)

Distribution of a medicine from one Member State to another by a pharmaceutical company independently of the marketing authorisation holder (European Medicines Agency, 2017j).

Parallel Importation (PI)

Importation from an EU Member State or a country within the European Economic Area of a medicinal product, which has a national Marketing Authorisation. The importer may be someone other than the importer appointed by the marketing authorisation holder of the product on the market. The medicinal product may then be parallel imported provided that the importer obtains a licence to market the product (European Commission, 2003c).

Package Leaflet (PL)

A leaflet containing information for the user which accompanies the medicinal product (European Commission, 2001b).

Periodic Safety Update Report (PSUR)

Pharmacovigilance documents intended to provide a safety update resulting in an evaluation of the impact of the reports on the risk-benefit balance of a medicinal product. They shall be submitted by marketing authorisation holders at defined time points during the post-authorisation phase (European Commission, 2012).

Personalised medicine

A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention (Nimmesgern et al, 2017).

Pharmaceutical alternative

Medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength (Committee for Medicinal Products for Human Use, 2010).

Pharmaceutical equivalence

Medicinal products containing the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards (Committee for Medicinal Products for Human Use, 2010).

Pharmaceutical Inspection Convention (PIC)

An international organisation which mutually recognises inspection reports on manufacturers (Brunner, 2004).

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

A scheme to improve cooperation between regulatory authorities and the pharmaceutical industry in the field of Good Manufacturing Practice (Brunner, 2004).

Pharmaceutics and Medical Devices Agency (PMDA)

Japan's drug regulatory agency whose mission is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices (Pharmaceutics and Medical Devices Agency, 2017).

Pharmacodynamics

Processes of bodily absorption, distribution, metabolism and excretion of medicines (International Conference on Harmonisation, 2007a).

Pharmacokinetics

Processes of bodily absorption, distribution, metabolism and excretion of medicines (International Conference on Harmonisation, 2007a).

Pharmacogenetics

Study of variations in DNA sequence as related to drug response (International Conference on Harmonisation, 2007b).

Pharmacogenomics

Study of variations of DNA and RNA characteristics as related to drug response (International Conference on Harmonisation, 2007b).

Pharmacovigilance (PhV)

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (European Medicines Agency and Heads of Medicines Agencies, 2014a).

Pharmacovigilance Risk Assessment Committee (PRAC)

Committee of the European Medicines Agency responsible for assessing all aspects of the risk management of medicines for human use (European Medicines Agency, 2013b).

Pharmacovigilance system master file (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorisation holder to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance (European Commission, 2001b).

Phase I Clinical Trial

A type of clinical study where a new medicine is given to humans for the first time, usually in healthy volunteers. It looks at the way the medicine is dealt with by the body, its main effects and main side effects (European Medicines Agency, 2017a).

Phase II Clinical Trial

A type of clinical study conducted after phase I studies to evaluate a medicine’s effects in a particular condition and to determine its common short-term side effects (European Medicines Agency, 2017a).

Phase III Clinical Trial

A type of clinical study usually conducted in a large group of patients to gather information about a medicine's efficacy and safety, to allow its benefits and risks to be evaluated (European Medicines Agency, 2017a).

Phase IV Clinical Trial

A type of clinical study that takes place after the authorisation of a medicine (European Medicines Agency, 2017a).

Pivotal Study

A study, normally phase III, designed and executed to get statistically significant evidence of efficacy and safety as required by health authorities for approval of new medicines approval (European Medicines Agency, 2001).

Post-authorisation efficacy report (PAES)

An efficacy study which is requested by a Competent Authority pursuant to at least one of the situations set out in this said regulation. The data resulting from such a PAES conducted within an authorised therapeutic indication are required to be submitted as they are considered important for complementing available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that is to be, or can only be, addressed post-authorisation. The results of the PAES have the potential to impact on the benefit-risk of the medicinal product or product information (European Commission 2001b; European Commission 2004b; European Medicines Agency, 2017a).

Post-authorisation safety study (PASS)

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product (European Commission, 2001b; European Medicines Agency; 2016a).

Power of attorney

A legal right of a separate person to act on behalf of the market authorization holder in matters related to a registered product (ICH, 2007a).

Precautions for storage

Special care to be taken into consideration to prevent contamination and deterioration of a medicinal product in relation to the effects of atmosphere, moisture, heat and light (ICH, 200a7).

Precautions for use

Special care to be exercised by prescriber and patient in the use of a medicinal product (ICH, 2007).

PRIority Medicines Scheme (PRIME)

Scheme developed by the European Medicines Agency to support the development of medicinal products of major public health interest through early and enhanced scientific and regulatory dialogue. The PRIME Scheme tool targets support to certain type of products eligible for accelerated assessment and falling within the scope of the centralised procedure. It builds also on existing regulatory tools in place within the EU legal framework, including scientific advice/protocol assistance (European Medicines Agency, 2016a).

Product Information

Documents providing officially approved information for healthcare professionals and patients on a medicine. The product information includes the summary of product characteristics, package leaflet and labelling (European Medicines Agency, 2017k).

Product-specific waiver

An exemption from the obligation to acquire data, through a paediatric investigation plan, in some or all subsets of the paediatric population for a given condition, route of administration and pharmaceutical form of a specified medicine (European Medicines Agency, 2017a).

Protocol

A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments (European Commission 2001b).

Protocol assistance

A type of scientific advice for companies developing orphan medicines (European Medicines Agency, 2014).

Public service obligation

The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question (European Commission, 2001b).

Q

Quality

Degree to which a set of inherent characteristics of a medicinal product fulfils requirements (European Committee for Standardisation; 2015).

Qualified Person (QP)

An authorised person with the requisite knowledge and experience to perform a given task (International Conference on Harmonisation, 2007a).

Qualified Person for Pharmacovigilance (QPPV)

A person appointed by a pharmaceutical company as the main person responsible for ensuring that the company (the product's Marketing Authorisation Holder or MAH) meets its legal obligations for the monitoring of the safety of a medicinal product on the market (European Commission, 2004b).

Quality Assurance (QA)

The total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use (European Commission, 2003b).

Quality Control (QC)

Quality Control enacts the SOP, monitoring and recording the activity of the process (European Commission, 2004c).

Quality Improvement

Part of quality management focused on increasing the ability to fulfil quality requirements (European Committee for Standardisation, 2015).

Quality Management System (QMS)

A quality management system comprises activities by which the organization identifies its objectives and determines the processes and resources required to achieve desired results (European Committee for

Standardisation, 2015).

Quality system

The organisational structure, defined responsibilities, procedures, processes and resources for implementing quality management, including all activities which contribute to quality, directly or indirectly (European Commission, 2006a).

R

Rapid Alert

An urgent notification from one competent authority to other authorities that a batch recall has been instituted in the country originating the rapid alert. (European Commission and European Medicines Agency, 2014).

Rapporteur

One of the two members of a committee or working party leading the assessment of an application (European Commission, 2004b).

Rare Disease

Life-threatening or chronically debilitating condition affecting no more than five in 10,000 people (European Commission, 2017d).

Raw material

Any substance, reagent or solvent which is intended for use in the production of an active substance and from which the active substance is not directly manufactured or extracted (European Commission, 2014a).

Reference Member State (RMS)

The Member State, which evaluates the marketing authorisation application dossier and prepares the assessment report on behalf of the Concerned Member States in Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) (Coordination Group for Mutual Recognition and Decentralised procedures - Human, 2006).

Referral

An evaluation conducted by a European Medicines Agency committee following a referral from the European Commission or a Member State. Referrals are used to address particular issues, such as safety concerns, to resolve disagreements between Member States on issues related to the authorisation of medicines or to give an opinion on an issue of Europe-wide interest (European Medicines Agency, 2017l).

Registry

Organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s) (Dreyer and Garner, 2009).

Regulatory Affairs

Application of defined regulatory principles to a given drug development or drug life cycle (Callre´us and Schneider, 2013).

Regulatory Authority

A body that carries out regulatory activities relating to medicines, including the processing of marketing authorisations, the monitoring of side effects, inspections, quality testing and monitoring the use of medicines (European Medicines Agency, 2017a).

Regulatory Science

The science (knowledge, tools, concepts, etc.) that underpins and evolves regulatory decision making (Callre´us and Schneider, 2013).

Renewal

An extension of the validity of a marketing authorisation, which can be for a fixed or indefinite period of time. Initial marketing authorisations are usually valid for five years (Coordination Group for Mutual Recognition and Decentralised procedures - Human, 2016).

Representative of the marketing authorisation holder

The person, commonly known as local representative, designated by the marketing authorisation holder to represent him in the Member State concerned (European Commission, 2001b).

Responsible Person (RP)

A local person who may be an individual or body corporate incorporated in and fully resident in a country and authorised to handle all issues related to a registered pharmaceutical product in the country (ICH, 2007a).

Risk

Combination of the likelihood of occurrence of harm and the degree of severity of the harm (International Conference on Harmonisation, 2005).

Risk Management Plan (RMP)

A detailed description of the activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicines (European Commission 2001b).

Risk Minimisation Measure (RMM)

A public health 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 the severity should it occur (European Medicines Agency and Heads of Medicines Agencies, 2017).

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (European Commission, 2001b).

S

Safe and Timely Access of Medicinal Products (STAMP)

Expert group set up to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation, as well as programmes and policies in this field. The STAMP exchanges views and information about the experience of Member States, examines national initiatives and identifies ways

to use more effectively the existing EU regulatory tools with the aim to further improve safe and timely access and availability of medicines for patients (European Commission, 2017e).

Safety

Prevention of errors and adverse effects to patients associated with health care (World Health Organisation, 2017b).

Safety signal

Information that arises 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, 2016).

Scientific Advice (SA)

Provision of advice to a company by the EMA on appropriate tests and studies required for the development of a medicine or on the quality of a medicine (European Medicines Agency, 2014).

Scientific Advice Working Party

A permanent working party of the Committee for Medicinal Products for Human Use (CHMP), in charge of Scientific Advice and Protocol Assistance for orphan medicinal products (European Medicines Agency, 2017m).

Secondary packaging

Secondary packing refers to additional packaging beyond the actual container in which a medicinal product is stored (European Commission, 2004c).

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect (European Commission, 2001b).

Signal assessment

Scientific evaluation of all the evidence available, including additional data from marketing authorisation holders, where applicable (European Medicines Agency, 2016).

Signal detection

Act of looking for and/or identifying signals using data from any source. Signal detection usually involves a combination of statistical methods and review of individual case safety reports, as well as any relevant source of information (e.g. scientific literature) (European Medicines Agency, 2016b).

Signal validation

Process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis (European Medicines Agency, 2016b).

Significant benefit

A clinically relevant advantage or a major contribution to patient care (European Commission, 2000).

Similar active substance

An identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism (European Commission, 2000).

Similar medicinal product

A medicinal product containing a similar active substance of substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication (European Commission, 2000).

Somatic cell-based medicine

A medicine containing cells or tissues that have been manipulated to change their biological characteristics, which is used to cure, diagnose or prevent a disease (European Commission, 2007).

Special warnings

A statement that inform in advance about a possible danger or unpleasant condition that is likely to happen when using a medicinal product (ICH, 2007a).

Specific Obligations

Requirements imposed on holders of conditional marketing authorisations or marketing authorisations granted under exceptional circumstances (CHMP, 2005).

Specification

A document giving a description of a starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and microbiological characteristics. A specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances (ICH, 2007a).

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial (European Commission, 2001b).

Stability

The capacity of an API or dosage form to remain over a period of time within specifications established to assure its identity, purity, strength, microbiological, biopharmaceutical and physico-chemical characteristics (International Conference on Harmonisation, 2007a).

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of the special functions. These provide a general framework enabling the efficient implementation and performance of the functions and activities for a particular process (European Commission, 2004c).

Strength

The content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight according to the dosage form (ICH, 2007a; European Commission, 2001b).

Summary of Product Characteristics (SmPC; SPC)

A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively (European Medicines Agency, 2017n).

Sunset clause

A legal provision stating that the marketing authorisation of a medicine will cease to be valid if the medicine is not placed on the market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years (European Medicines Agency, 2017o).

Suspected Defective Product

A medicinal product about which a report has been received suggesting that it is not of the correct quality, as defined by its Marketing Authorisation (European Commission and European Medicines Agency, 2014).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any unfavourable medical occurrence in a clinical research study participant, including any abnormal sign, symptom or disease, temporally associated with the participants' involvement in the research and which is suspected to be related to the investigational medicinal product under research (European Commission, 2001b).

T

Therapeutic equivalence

Two pharmaceutical products are substitutable if they are pharmaceutically equivalent or alternatives and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro studies (ICH, 2007a).

Tissue-engineered product

A medicine containing engineered cells or tissues, which is intended to regenerate, repair or replace a human tissue (European Commission, 2007).

Top Management

Person or group of people who directs and controls an organisation at the highest level (European Committee for Standardisation, 2015).

Transfer of Marketing Authorisation Holder

A change to a marketing authorisation where the ownership of a marketing authorisation is moved from one marketing-authorisation holder to another (European Commission, 2008a).

Type IA variation

A minor change to a marketing authorisation that has a minimal or no impact on the quality, safety or efficacy of the medicine and does not require prior approval before implementation by the marketing authorisation holder (European Commission, 2008a).

Type IB variation

A minor change to a marketing authorisation that the marketing-authorisation holder must notify to the regulatory authority before implementation, but which does not require formal approval (European Commission, 2008a).

Type II variation

A major change to a marketing authorisation that may have a significant impact on the quality, safety or efficacy of a medicine, but does not involve a change to the active substance, its strength or the route of administration. Type II variations require a formal approval (European Commission, 2008a).

U

United Nations Educational, Scientific and Cultural Organisation (UNESCO)

An agency of the United Nations responsible for coordinating international cooperation in education, science, culture and communication (United Nations Educational, Scientific and Cultural Organisation, 2017).

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics (European Commission, 2001b).

Unique identifier

Safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product (European Commission, 2016).

Unmet medical need

Condition for which there is no available effective treatment (Food and Drug Administration, 2017b).

Urgent Safety restriction

An interim change in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product (European Commission, 2008a).

V

Variation

Amendment to the terms of decision granting marketing authorisation for a medicinal product, including summary of product characteristics and any conditions, obligations, or restrictions affecting marketing authorisation, or changes to labelling or package leaflet associated with changes to summary of product characteristics (European Commission, 2008a).

W

Well-established use (WEU)

When an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature (European Commission, 2001b).

Wholesale distribution

All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned (European Commission, 2001b).

Withdrawal

Total removal of the product from the market (International Conference on Harmonisation, 2007a).

Working Group of Enforcement Officers (WGEO)

A working group established by the Heads of Medicines Agencies to contribute to the protection of human and animal health and welfare, with the aim to: promote liaison and co-operation between Member States and agencies with the purpose of sharing information; identify emerging threats to the legal manufacturing and distribution chain; coordinate communications and initiatives, exchanging information with relevant working parties/groups and organisations; provide a valuable network for European counterparts to build trust, share experience, best practice and expertise relating to pharmaceutical crime; and deliver a practical training platform – largely related to the four work-streams: wholesale and distribution; Internet (illegal supply of medicines); falsified medicines and training and education (HMA, 2017f).

Working Party

A group of European experts that can be consulted by the European Medicines Agency's committees on scientific issues in their area of expertise. Working parties are often given tasks linked to the evaluation of applications and the drafting or revision of guidance (European Medicines Agency, 2017a).

Work-sharing

Submission of a single application for a variation that affects more than one marketing authorisation from the same marketing authorisation holder (European Medicines Agency 2017a).

World Health Organisation (WHO)

An agency of the United Nations that is concerned with international public health (WHO, 2017c).

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APPENDIX 2

Clinical development programmes: Oncology therapeutic area

CONDITIONAL MARKETING AUTHORISATIONS	
2006	**2007**
Sutent	**Vectibix**
Phase II A6181006 • Single arm • Non-randomised • Open-label • 50mg daily for 4 weeks in 6-week cycles • Metastatic renal cell carcinoma not amenable to therapy with curative intent + failure during or intolerance to previous cytokine therapy • Sample size – 106 • Primary endpoint – Objective response rate **Phase II RTKC- 0511-014** • Single arm • Non-randomised • Open-label • 50mg daily for 4 weeks in 6-week cycles • Metastatic renal cell carcinoma not amenable to therapy with curative intent + failure during or intolerance to previous cytokine therapy • Sample size – 63 • Primary endpoint – Objective response rate **Phase III A6181004** • Multiple Arm • Randomised • Double blind • 50mg daily for 4 weeks in 6-week cycles • Patients with malignant gastrointestinal stromal tumors who had tumours that were resistant to imatinib, or who were intolerant of imatinib • Sample size – 207 • Primary endpoint – Time to progression	**Phase III 20020408** • Multiple arm • Randomised • Open-label • 6mg/kg every two weeks • Patients with estimated epidermal growth factor receptor expressing metastatic colorectal carcinoma that has progressed on or after treatment with a fluoropyrimidine, irinotecan, and oxaliplatin • Sample size – 231 • Primary endpoint – Progression Free Survival
2008	**2010**
Tyverb	**Arzerra**
Phase III EGF10015 1 • Multiple arm • Randomised • Open-label • 1250mg once daily • ErbB2 over-expressing, locally advanced or metastatic breast cancer patients, who were progressing after prior treatment that included anthracyclines, taxanes and trastuzumab • Sample size – 198 • Primary endpoint – Median time to progression	**Phase I/II Hx- CD20- 402** • Multiple arm • Non-randomised • Open-label • Group A: 100mg×1, 500mg×3 (weekly) Group B: 300mg×1, 1000mg×3 (weekly) Group C: 500mg×1, 2000mg×3 (weekly) • Relapsed/refractory chronic lymphoid leukemia • Sample size – 33 • Primary endpoint – Objective response rate **Phase II Hx- CD20- 406** • Single arm • Non-randomised • Open-label • 300mg × 1; 2000mg × 7 (weekly) 2000mg × 4 (every 4 weeks) • Subjects with chronic lymphoid leukemia refractory to fludarabine and alemtuzumab,

	or refractory to fludarabine and inappropriate for alemtuzumab due to bulky lymphadenopathy • Sample size – 154 • Primary endpoint – Objective response rate
2010	**2011**
Votrient	**Votubia**
Phase III VEG105192 • Multiple arm • Randomised • Double blind • 800mg once daily • patients with advanced renal cell carcinoma who had received no prior systemic treatment or only received prior cytokine treatment for advanced disease • Sample size – 290 • Primary endpoint – median progression free survival	**Phase II C2485** • Single arm • Non-randomised • Open-label • titrated to achieve target concentrations of 5-15 ng/mL • confirmed diagnosis of tuberous sclerosis complex and radiological evidence of serial subependymal giant cell astrocytoma growth • Sample size – 28 • Primary endpoint – Change from baseline **Phase III M2301** • Multiple arm • Randomised • Double bline • titrated to achieve target concentrations of 5-15 ng/mL • patients diagnosed with tuberous sclerosis complex associated subependymal giant cell astrocytomas and have radiological evidence of one of the following three conditions prior to randomization: 1) serial growth, or 2) presence of a new subependymal giant cell astrocytoma lesion, or 3) new or worsening hydrocephalus. • Sample size – 78 • Primary endpoint – Objective Response rate
2012	**2012**
Adcetris	**Xalkori**
Phase II SG035-0003 • Single-arm • Non-randomised • Open-label • 1.8 mg/kg IV q3 wk, 16 cycles • Patients with relapsed or refractory CD30+ Hodgkin lymphoma post autologous stem cell transplant • Sample size – 102 • Primary endpoint – Overall response rate **Phase II SG035-0004** • Single-arm • Non-randomised • Open-label • 1.8 mg/kg IV q3 wk, 16 cycles • Patients with relapsed or refractory Systemic Anaplastic Large Cell Lymphoma (sALCL) • Sample size – 58 • Primary endpoint – Overall response rate	**Phase I/II A8081001** • Single arm • Non-randomised • Open-label • 250 mg twice daily in continuous 28-day cycles • previously treated ALK- positive advanced non-small cell lung cancer • Sample size – 149 • Primary endpoint – PK/PD, Safety **Phase II A8081005** • Single arm • Non-randomised • Open-label • 250 mg twice daily in continuous 21-day cycles • previously treated ALK- positive advanced non-small cell lung cancer population • Sample size – 439 • Primary endpoint – Objective response rate

	Phase III 1007 • Multiple arm • Randomised • Open-label • daily crizotinib at a starting dose of 250 mg twice daily in 3-week cycles • ALK-positive, advanced non-small cell lung cancer patients who received only one prior chemotherapy regimen that was platinum-based • Sample size – 173 • Primary endpoint – progression free survival
2012	**2012**
Pixuvri	**Caprelsa**
Phase III PIX301 • Multiple arm • Randomised • Partial blinding • 85 mg/m^2 on days 1, 8, and 15 of 28- day cycles • Patients with Relapsed/Refractory Aggressive (de novo or transformed) Non- Hodgkin's Lymphoma (3rd line), with measurable disease, prior treatment with ≥ 2 chemotherapy regimen and sensitivity to the last anthracycline/ anthracenedione regimen • Sample size – 70 • Primary endpoint – Complete response rate	**Phase III D4200C00058** • Multiple arm • Randomised • Double blind • 300mg once daily • Subjects with unrespectable locally advanced or metastatic hereditary or sporadic medullary thyroid cancer • Sample size – 231 • Primary endpoint – median progression free survival
2013	**2013**
Bosulif	**Erivedge**
Phase I/II 3160A4-200-WW • Single arm • Non-randomised • Open-label • 500mg daily • Chronic-phase, accelerated-phase, and blastic-phase chronic myeloid leukemia patients who may not be candidates for treatment with at least 1 of the currently approved tyrosine kinase inhibitor due to intolerance, mutations, or comorbidities • Sample size – 52 • Primary endpoint – Objective response rate	**Phase II SHH4476g** • Single arm • Non-randomised • Open-label • 150mg daily • Patients with advanced basal cell carcinoma • Sample size – 104 • Primary endpoint – Objective response rate
2014	**2015**
Cometriq	**Zykadia**
Phase III XL184-301 • Multiple arm • Non-randomised • Double blind • 138mg qd • Patients with unresectable locally advanced or metastatic medullary thyroid carcinoma, experiencing disease progression within 14 months from previous radiological assessment • Sample size – 219 • Primary endpoint – progression free survival	**Phase I X2101** • Multiple arm • Non-randomised • Open-label • 50-750mg once daily continuously • adult patients with tumors characterized by genetic abnormalities in ALK • Sample size – 246 • Primary endpoint – n/a

	Phase II A2201 • Single arm • Non-randomised • Open-label • 750mg once daily • patients with ALK-positive non-small cell lung cancer who have progressed on crizotinib • Sample size – 140 • Primary endpoint – Overall response rate **Phase II A2203** • Single arm • Non-randomised • Open-label • 750mg once daily • Crizotinib naïve adult patients with ALK-activated non-small cell lung cancer • Sample size – 124 • Primary endpoint – Overall response rate
2015	**2016**
Blincyto	**Darzalex**
Phase II MT103-211 • Single arm • Non-randomised • Open-label • 9-28 ug/day • subjects with relapsed/refract ory B-precursor acute lymphoblastic leukemia • Sample size – 189 • Primary endpoint – Complete remission	**Phase I/II GEN501** • Multiple arm • Randomised • Open-label • 8 or 16mg/kg • MM patients relapsed from or refractory to at least 2 different cytoreductive therapies and without further treatment options • Sample size – 104 • Primary endpoint – objective response rate **Phase II MMY2002** • Multiple arm • Randomised • Open-label • 8 or 16mg/kg • Multiple mlyeloma patients who have received at least 3 prior lines of therapy (incl. protease inhibitors and immunomodulatory drug) or double refractory to protease inhibitors and immunomodulatory drug • Sample size – 124 • Primary endpoint – Objective response rate
2016	**2016**
Lartruvo	**Ninlaro**
Phase I/II I5B-IE-JGDG IMCL CP15-0806 • Multiple arm • Phase 1b non-randomised / Phase 2 randomised • Open-label • Phase1b – Olara: 15mg/kg, Days 1 and 8, Q3W; Phase2, Arm A - Olara: 15 mg/kg, Days 1 and 8 + Dox: 75 mg/m2, Day 1, Q3W; Phase 2, Arm B - Dox: 75 mg/m2, Day 1, Q3W • Advanced soft tissue sarcoma	**Phase III C16010, 2011-005496-17** • Multiple arm • Randomised • Double blind • 4 mg PO once weekly on days 1,8 and 15 in addition to Lenalidomide 25 mg on days 1 through 21 and Dexamethasone 40 mg on days 1,8,15 and 22 of a 28-days cycle • relapsed/refractory multiple myeloma who have received at least one prior therapy • Sample size – 722

• Sample size – 133 • Primary endpoint – progression free survival	• Primary endpoint – progression free survival
2016	**2016**
Tagrisso	**Zalmoxis**
Phase II AURA extension • Single arm • Non-randomised • Open-label • 80mg daily • Pre-treated patients with centrally- confirmed T790M mutation-positive non-small cell lung cancer • Sample size – 201 • Primary endpoint – Objective response rate **Phase II AURA 2** • Single arm • Non-randomised • Open-label • 80mg daily • Pre-treated patients with centrally- confirmed T790M mutation-positive non-small cell lung cancer • Sample size – 210 • Primary endpoint – Objective response rate	**Phase I/II TK007** • Non-randomised • Open-label • 4 monthly • IV infusions given first dose: 1x106 or 1x107 cells/kg; second dose: 1x107 cells/kg; third dose: 1x106 cells/kg plus interleukin-2 (1x106 IU/m2 subcutaneously for five days); - fourth dose: 1x107 cells/kg plus interleukin-2 (1x106 IU/m2 subcutaneously for five days) • infusion of donor lymphocytes transduced with the suicide gene HSV-TK, after transplantation of allogeneic T-depleted stem cells from a haploidentical donor in patients with hematological malignancies • Sample size – 57 • Primary endpoint – immune reconstitution
2016	
Venclyxto	
Phase II M13-982 • Single arm • Non-randomised • Open-label • 400 mg qd • Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukaemia Harboring the 17p Deletion • Sample size – 107 • Primary endpoint – objective response rate	

EXCEPTIONAL MARKETING AUTHORISATIONS	
2001	**2004**
Onsenal	**Xagrid**
Phase II IQ4-99-06-001 • Multiple arm • Randomised • Double-blind • Familial Polyposis with gastrointestinal disease • Sample size – 83 • Primary endpoint – Change from baseline	**Study 700-012** • Multi-centre • Open-label • Non-randomised • Essential Thrombocythaemia (ET) or Polycythemia Vera (PV) patients requiring platelet reduction • Sample size – 44 • Primary endpoint – complete response, partial response, objective response rate **Phase II 700-014** • Multi-centre • Open-label • Randomised • Subjects with thrombocythaemia • Sample size – 498 • Primary endpoint – complete response, partial response, objective response rate **Study 700-099** • Multi-centre • Open-label • Non-randomised • Subjects with thrombocythaemia • Sample size – 455 • Primary endpoint – complete response, partial response, objective response rate **Study 13970-301** • Multi-centre • Open-label • ET patients 18 years of age or older previously treated with a platelet-reducing agent but who had a medical indication to change therapy, or who were contraindicated for using currently available platelet-reducing therapy • Sample size – 934 • Primary endpoint – Complete Response
2006	**2007**
Evoltra	**Atriance**
Phase II CLO-212 • Open-label • Single-arm • Paediatric patients with acute lymphoblastic leukemia who were not eligible for therapy of higher curative potential, and who were in second or subsequent relapse and/or refractory • Sample size – 40 • Primary endpoint – Overall remission rate	**Phase I/II PGA A2001** • Open-label • Non-randomised • Multiple arm • 4 groups [adult leukemia (stratum 1), paediatric leukemia (stratum 2), adult lymphoma (stratum 3), and paediatric lymphoma (stratum 4)] • Sample size – 93 • Primary endpoint – Complete response **Phase II PGA A2002** • Open-label • Multicenter

	• Non-randomised • Patients with refractory hematologic malignancies: (17 adult; 10 paediatric patients) • Sample size - 27 • Primary endpoint- Complete response
2008	**2009**
Ceplene	**Ilaris**
Phase III MP-MA-0201 • Multicentre • Randomised • Open-label • 2-arm study • acute myeloid leukaemia in first or subsequent complete remission • Sample size – 320 • Primary endpoint – progression free survival	**Study D2304** • Multicenter • Multinational • Open-label • Randomised • Adults and children with Muckle-Wells Syndrome • Sample size – 104 • Primary endpoint – change from baseline
2009	
Rilonacept Regeneron	
Phase III ILIT-AI-0505 • Multicentre • Randomised • Double-blind • Placebo-controlled study • Sample size – 47 • Primary endpoint – change from baseline	

APPENDIX 3

List of ATC codes covered by centrally authorised products extracted 15/06/2015

ATC Code	Therapeutic subgroup	Chemical substance
A02BC02	Drugs for acid related disorders	Pantoprazole
A02BC05	Drugs for acid related disorders	Esomeprazole
A04AA02	Antiemetics and antinauseants	Granisetron
A04AA05	Antiemetics and antinauseants	Palonosetron Hydrochloride
A04AD12	Antiemetics and antinauseants	Aprepitant
A05AA03	Bile and liver therapy	Cholic Acid
A06AH01	Laxatives	Methylnaltrexone Bromide
A06AH03	Laxatives	Naloxegol Oxalate
A06AX04	Laxatives	Linaclotide
A06AX05	Laxatives	Prucalopride Succinate
A07AA12	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	Fidaxomicin
A08AA62	Antiobesity preparations, excluding diet products	Bupropion Hydrochloride / Naltrexone Hydrochloride
A08AB01	Antiobesity preparations, excluding diet products	Orlistat
A10	Drugs used in diabetes	Dulaglutide
A10AB01	Drugs used in diabetes	Human Insulin
A10AB05	Drugs used in diabetes	Insulin Aspart
A10AB06	Drugs used in diabetes	Insulin Glulisine
A10ABCD01	Drugs used in diabetes	Insulin Human
A10AC01	Drugs used in diabetes	Insulin Human
A10AC04	Drugs used in diabetes	Insulin Lispro
A10AD01	Drugs used in diabetes	Insulin Human
A10AD05	Drugs used in diabetes	Insulin Aspart
A10AD06	Drugs used in diabetes	Insulin Degludec / Insulin Aspart
A10AE04	Drugs used in diabetes	Insulin Glargine
A10AE05	Drugs used in diabetes	Insulin Detemir
A10AE06	Drugs used in diabetes	Insulin Degludec
A10BD05	Drugs used in diabetes	Pioglitazone / Metformin Hydrochloride
A10BD06	Drugs used in diabetes	Pioglitazone / Glimepiride
A10BD07	Drugs used in diabetes	Sitagliptin / Metformin Hydrochloride
A10BD08	Drugs used in diabetes	Vildagliptin / Metformin Hydrochloride
A10BD09	Drugs used in diabetes	Alogliptin / Pioglitazone
A10BD10	Drugs used in diabetes	Metformin Hydrochloride /Saxagliptin Hydrochloride
A10BD11	Drugs used in diabetes	Linagliptin / Metformin
A10BD13	Drugs used in diabetes	Alogliptin Benzoate / Metformin Hydrochloride
A10BD15	Drugs used in diabetes	Metformin Hydrochloride / Dapagliflozin Propanediol Monohydrate
A10BD16	Drugs used in diabetes	Canagliflozin / Metformin Hydrochloride
A10BD20	Drugs used in diabetes	Empagliflozin / Metformin
A10BG03	Drugs used in diabetes	Pioglitazone Hydrochloride
A10BH01	Drugs used in diabetes	Sitagliptin
A10BH02	Drugs used in diabetes	Vildagliptin
A10BH03	Drugs used in diabetes	Saxagliptin

ATC Code	Therapeutic subgroup	Chemical substance
A10BH04	Drugs used in diabetes	Alogliptin
A10BH05	Drugs used in diabetes	Linagliptin
A10BX02	Drugs used in diabetes	Repaglinide
A10BX03	Drugs used in diabetes	Nateglinide
A10BX04	Drugs used in diabetes	Exenatide
A10BX07	Drugs used in diabetes	Liraglutide
A10BX09	Drugs used in diabetes	Dapagliflozin Propanediol Monohydrate
A10BX10	Drugs used in diabetes	Lixisenatide
A10BX11	Drugs used in diabetes	Canagliflozin
A10BX12	Drugs used in diabetes	Empagliflozin
A10BX13	Drugs used in diabetes	Albiglutide
A11HA08	Vitamins	Tocofersolan
A16AA04	Other alimentary tract and metabolism products	Mercaptamine Bitartrate
A16AA05	Other alimentary tract and metabolism products	Carglumic Acid
A16AA06	Other alimentary tract and metabolism products	Betaine Anhydrous
A16AB	Other alimentary tract and metabolism products	Galsulfase
A16AB02	Other alimentary tract and metabolism products	Imiglucerase
A16AB03	Other alimentary tract and metabolism products	Agalsidase Alfa
A16AB04	Other alimentary tract and metabolism products	Agalsidase Beta
A16AB05	Other alimentary tract and metabolism products	Laronidase
A16AB07	Other alimentary tract and metabolism products	Alglucosidase Alfa
A16AB09	Other alimentary tract and metabolism products	Idursulfase
A16AB10	Other alimentary tract and metabolism products	Velaglucerase Alfa
A16AB12	Other alimentary tract and metabolism products	Recombinant Human N-Acetylgalactosamine-6-Sulfatase (Rhgalns)
A16AX03	Other alimentary tract and metabolism products	Sodium Phenylbutyrate
A16AX04	Other alimentary tract and metabolism products	Nitisinone
A16AX05	Other alimentary tract and metabolism products	Zinc
A16AX06	Other alimentary tract and metabolism products	Miglustat
A16AX07	Other alimentary tract and metabolism products	Sapropterin Dihydrochloride
A16AX08	Other alimentary tract and metabolism products	Teduglutide
A16AX10	Other alimentary tract and metabolism products	Eliglustat
B01	Antithrombotic agents	Cangrelor
B01AB02	Antithrombotic agents	Antithrombin Alfa
B01AC03	Antithrombotic agents	Clopidogrel Hydrogen Sulphate

ATC Code	Therapeutic subgroup	Chemical substance
B01AC04	Antithrombotic agents	Clopidogrel
B01AC05	Antithrombotic agents	Clopidogrel Besilate
B01AC06	Antithrombotic agents	Clopidogrel Hydrochloride
B01AC11	Antithrombotic agents	Iloprost
B01AC16	Antithrombotic agents	Eptifibatide
B01AC22	Antithrombotic agents	Prasugrel
B01AC24	Antithrombotic agents	Ticagrelor
B01AC30	Antithrombotic agents	Clopidogrel / Acetylsalicylic Acid
B01AD08	Antithrombotic agents	Reteplase
B01AD11	Antithrombotic agents	Tenecteplase
B01AD12	Antithrombotic agents	Human Protein C
B01AE06	Antithrombotic agents	Bivalirudin
B01AE07	Antithrombotic agents	Dabigatran Etexilate Mesilate
B01AF01	Antithrombotic agents	Rivaroxaban
B01AF02	Antithrombotic agents	Apixaban
B01AX01	Antithrombotic agents	Defibrotide
B01AX05	Antithrombotic agents	Fondaparinux Sodium
B02BC	Antihemorrhagics	Human Fibrinogen / Human Thrombin
B02BC30	Antihemorrhagics	Human Fibrinogen / Human Thrombin
B02BD02	Antihemorrhagics	Octocog Alfa
B02BD04	Antihemorrhagics	Human Coagulation Factor Ix
B02BD06	Antihemorrhagics	Human Coagulation Factor Viii / Von Willebrand Factor
B02BD08	Antihemorrhagics	Eptacog Alfa (Activated)
B02BD09	Antihemorrhagics	Nonacog Alfa
B02BD11	Antihemorrhagics	Catridecacog
B02BX04	Antihemorrhagics	Romiplostim
B02BX05	Antihemorrhagics	Eltrombopag Olamine
B03	Antianemic preparations	Ferumoxytol
B03XA01	Antianemic preparations	Epoetin Alfa
B03XA02	Antianemic preparations	Darbepoetin Alfa
B03XA03	Antianemic preparations	Methoxy Polyethylene Glycol-Epoetin Beta
B06AC01	Other hematological agents	C1 Inhibitor (Human)
B06AC04	Other hematological agents	Conestat Alfa
C01BD07	Cardiac therapy	Dronedarone
C01BG11	Cardiac therapy	Vernakalant Hydrochloride
C01EB16	Cardiac therapy	Ibuprofen
C01EB17	Cardiac therapy	Ivabradine Hydrochloride
C01EB18	Cardiac therapy	Ranolazine
C01EB19	Cardiac therapy	Icatibant
C01EB21	Cardiac therapy	Regadenoson
C02KX01	Antihypertensives	Bosentan Monohydrate
C02KX02	Antihypertensives	Ambrisentan
C02KX04	Antihypertensives	Macitentan

ATC Code	Therapeutic subgroup	Chemical substance
C02KX05	Antihypertensives	Riociguat
C03XA01	Diuretics	Tolvaptan
C07AA05	Beta blocking agents	Propranolol Hydrochloride
C09CA04	Agents acting on the renin-angiotensin system	Irbesartan
C09CA07	Agents acting on the renin-angiotensin system	Telmisartan
C09CA09	Agents acting on the renin-angiotensin system	Azilsartan Medoxomil
C09DA04	Agents acting on the renin-angiotensin system	Irbesartan / Hydrochlorothiazide
C09DA07	Agents acting on the renin-angiotensin system	Telmisartan / Hydrochlorothiazide
C09DB01	Agents acting on the renin-angiotensin system	Amlodipine (As Besylate) / Valsartan
C09DB04	Agents acting on the renin-angiotensin system	Telmisartan / Amlodipine
C09DX01	Agents acting on the renin-angiotensin system	Amlodipine / Valsartan / Hydrochlorothiazide
C09XA02	Agents acting on the renin-angiotensin system	Aliskiren
C09XA52	Agents acting on the renin-angiotensin system	Aliskiren / Hydrochlorothiazide
C09XA53	Agents acting on the renin-angiotensin system	Aliskiren / Amlodipine
C10AC04	Lipid modifying agents	Colesevelam
C10AX10	Lipid modifying agents	Alipogene Tiparvovec
C10AX12	Lipid modifying agents	Lomitapide
C10BA03	Lipid modifying agents	Fenofibrate / Pravastatin
C10BA04	Lipid modifying agents	Fenofibrate / Simvastatin
D02BB02	Emollients and protectives	Afamelanotide
D03BA03	Preparations for treatment of wounds & ulcers	Concentrate Of Proteolytic Enzymes Enriched In Bromelain
D06AX13	Antibiotics and chemotherapeutics for dermatological use	Retapamulin
D06BB10	Antibiotics and chemotherapeutics for dermatological use	Imiquimod
D06BX02	Antibiotics and chemotherapeutics for dermatological use	Ingenol Mebutate
D11AH01	Other dermatological preparations	Tacrolimus
D11AX	Other dermatological preparations	Eflornithine
D11AX21	Other dermatological preparations	Brimonidine Tartrate
G02CX01	Other gynecologicals	Atosiban Acetate
G03AA13	Sex hormones and modulators of the genital system	Norelgestromin / Ethinyl Estradiol
G03AA14	Sex hormones and modulators of the genital system	Nomegestrol Acetate / Estradiol
G03AD02	Sex hormones and modulators of the genital system	Ulipristal
G03CX	Sex hormones and modulators of the genital system	Oestrogens Conjugated / Bazedoxifene
G03GA05	Sex hormones and modulators of the genital system	Follitropin Alfa

ATC Code	Therapeutic subgroup	Chemical substance
G03GA06	Sex hormones and modulators of the genital system	Follitropin Beta
G03GA07	Sex hormones and modulators of the genital system	Lutropin Alfa
G03GA08	Sex hormones and modulators of the genital system	Choriogonadotropin Alfa
G03GA09	Sex hormones and modulators of the genital system	Corifollitropin Alfa
G03XB02	Sex hormones and modulators of the genital system	Ulipristal Acetate
G03XC01	Sex hormones and modulators of the genital system	Raloxifene Hydrochloride
G03XC02	Sex hormones and modulators of the genital system	Bazedoxifene
G03XC05	Sex hormones and modulators of the genital system	Ospemifene
G04BD04	Urologicals	Oxybutynin
G04BD10	Urologicals	Darifenacin Hydrobromide
G04BD11	Urologicals	Fesoterodine Fumarate
G04BD12	Urologicals	Mirabegron
G04BE03	Urologicals	Sildenafil
G04BE08	Urologicals	Tadalafil
G04BE09	Urologicals	Vardenafil
G04BE10	Urologicals	Avanafil
G04CA04	Urologicals	Silodosin
H01AB01	Pituitary and hypothalamic hormones	Thyrotropin Alfa
H01AC01	Pituitary and hypothalamic hormones	Somatropin
H01AC03	Pituitary and hypothalamic hormones	Mecasermin
H01AX01	Pituitary and hypothalamic hormones	Pegvisomant
H01CB05	Pituitary and hypothalamic hormones	Pasireotide
H01CC01	Pituitary and hypothalamic hormones	Ganirelix
H01CC02	Pituitary and hypothalamic hormones	Cetrorelix
H02AB09	Corticosteroids for systemic use	Hydrocortisone
H05AA02	Calcium homeostasis	Teriparatide
H05BX01	Calcium homeostasis	Cinacalcet
J01	Antibacterials for systemic use	Tedizolid Phosphate
J01AA12	Antibacterials for systemic use	Tigecycline
J01DF01	Antibacterials for systemic use	Aztreonam Lysine
J01DH03	Antibacterials for systemic use	Ertapenem Sodium
J01DI02	Antibacterials for systemic use	Ceftaroline Fosamil
J01FA15	Antibacterials for systemic use	Telithromycin
J01GB01	Antibacterials for systemic use	Tobramycin
J01MA12	Antibacterials for systemic use	Levofloxacin
J01XA03	Antibacterials for systemic use	Telavancin
J01XA04	Antibacterials for systemic use	Dalbavancin HCl
J01XA05	Antibacterials for systemic use	Oritavancin Diphosphate
J01XX09	Antibacterials for systemic use	Daptomycin
J02AB02	Antimycotics for systemic use	Ketoconazole

ATC Code	Therapeutic subgroup	Chemical substance
J02AC03	Antimycotics for systemic use	Voriconazole
J02AC04	Antimycotics for systemic use	Posaconazole
J02AX04	Antimycotics for systemic use	Caspofungin
J02AX05	Antimycotics for systemic use	Micafungin
J02AX06	Antimycotics for systemic use	Anidulafungin
J04A	Antimycobacterials	Bedaquiline Fumarate
J04AA01	Antimycobacterials	Para-Aminosalicylic Acid
J04AK06	Antimycobacterials	Delamanid
J05	Antivirals for systemic use	Darunavir / Cobicistat
J05AB04	Antivirals for systemic use	Ribavirin
J05AE	Antivirals for systemic use	Telaprevir
J05AE01	Antivirals for systemic use	Saquinavir
J05AE02	Antivirals for systemic use	Indinavir Sulphate
J05AE03	Antivirals for systemic use	Ritonavir
J05AE07	Antivirals for systemic use	Fosamprenavir Calcium
J05AE08	Antivirals for systemic use	Atazanavir Sulphate
J05AE09	Antivirals for systemic use	Tipranavir
J05AE10	Antivirals for systemic use	Darunavir
J05AE14	Antivirals for systemic use	Simeprevir
J05AF04	Antivirals for systemic use	Stavudine
J05AF05	Antivirals for systemic use	Lamivudine
J05AF06	Antivirals for systemic use	Abacavir
J05AF07	Antivirals for systemic use	Tenofovir Disoproxil Fumarate
J05AF08	Antivirals for systemic use	Adefovir Dipivoxil
J05AF09	Antivirals for systemic use	Emtricitabine
J05AF10	Antivirals for systemic use	Entecavir
J05AF11	Antivirals for systemic use	Telbivudine
J05AG01	Antivirals for systemic use	Nevirapine
J05AG03	Antivirals for systemic use	Efavirenz
J05AG04	Antivirals for systemic use	Etravirine
J05AG05	Antivirals for systemic use	Rilpivirine Hydrochloride
J05AH02	Antivirals for systemic use	Oseltamivir
J05AR01	Antivirals for systemic use	Lamivudine / Zidovudine
J05AR02	Antivirals for systemic use	Abacavir / Lamivudine
J05AR03	Antivirals for systemic use	Emtricitabine / Tenofovir Disoproxil Fumarate
J05AR04	Antivirals for systemic use	Abacavir (As Sulfate) / Lamivudine / Zidovudine
J05AR06	Antivirals for systemic use	Efavirenz / Emtricitabine / Tenofovir Disoproxil Fumarate
J05AR08	Antivirals for systemic use	Emtricitabine / Rilpivirine Hydrochloride /Tenofovir Disoproxil Fumarate
J05AR09	Antivirals for systemic use	Elvitegravir / Cobicistat / Emtricitabine / Tenofovir Disoproxil Fumarate
J05AR10	Antivirals for systemic use	Lopinavir / Ritonavir
J05AR13	Antivirals for systemic use	Abacavir Sulfate / Dolutegravir Sodium / Lamivudine

ATC Code	Therapeutic subgroup	Chemical substance
J05AR16	Antivirals for systemic use	Lamivudine / Raltegravir Potassium
J05AX07	Antivirals for systemic use	Enfuvirtide
J05AX08	Antivirals for systemic use	Raltegravir
J05AX09	Antivirals for systemic use	Maraviroc
J05AX11	Antivirals for systemic use	Elvitegravir
J05AX12	Antivirals for systemic use	Dolutegravir
J05AX14	Antivirals for systemic use	Daclatasvir Dihydrochloride
J05AX15	Antivirals for systemic use	Sofosbuvir
J06BA	Immune sera and immunoglobulins	Human Normal Immunoglobulin
J06BA01	Immune sera and immunoglobulins	Human Normal Immunoglobulin (Scig)
J06BA02	Immune sera and immunoglobulins	Human Normal Immunoglobulin
J06BB04	Immune sera and immunoglobulins	Human Hepatitis-B Immunoglobulin
J06BB16	Immune sera and immunoglobulins	Palivizumab
J07AE01	Vaccines	Recombinant Cholera Toxin B Subunit / Vibrio Cholerae 01
J07AH08	Vaccines	Meningococcal Group A, C, W-135 And Y Conjugate Vaccine
J07AH09	Vaccines	Recombinant Neisseria Meningitidis Group-B Nhba Fusion Protein /Recombinant Neisseria Meningitidis Group-B Nada Protein /Recombinant Neisseria Meningitidis Group B Fhbp Fusion Protein /Outer Membrane Vesiclesfrom Neisseria Meningitidis Group-B Strain Nz98 / 254 Measured As Amount Of Total Protein Containing The Pora P1.4
J07AL02	Vaccines	Pneumococcal Polysaccharide Serotype 4 /Pneumococcal Polysaccharide Serotype 6B /Pneumococcal Polysaccharide Serotype 9V /Pneumococcal Polysaccharide Serotype 14 / Pneumococcal Oligosaccharide Serotype 18C /Pneumococcal Polysaccharide Serotype 19F /Pneumococcal Polysaccharide Serotype 23F
J07AL52	Vaccines	Pneumococcal Polysaccharide Serotype 1 /Pneumococcal Polysaccharide Serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F /Pneumococcal Polysaccharide Serotype 14 /Pneumococcal Polysaccharide Serotype 18C /Pneumococcal Polysaccharide Serotype 19F / Pneumococcal Polysaccharide Serotype 23F /Pneumococcal Polysaccharide Serotype 4 /Pneumococcal Polysaccharide Serotype 5 /Pneumococcal Polysaccharide Serotype 6B /Pneumococcal Polysaccharide Serotype 7F /Pneumococcal Polysaccharide Serotype 9V
J07BA02	Vaccines	Japanese-Encephalitis Virus, Inactivated (Attenuated Strain Sa14-14-2 Grown In Vero Cells)
J07BB01	Vaccines	Whole Virion, Inactivated Containing Antigen: A/California/07/2009 (H1N1)V
J07BB02	Vaccines	Split Influenza Virus, Inactivated, Containing Antigen: A/Vietnam/1194/2004 (H5N1) Like Strain Used (Nibrg-14)

ATC Code	Therapeutic subgroup	Chemical substance
J07BB03	Vaccines	Influenza Virus Type A, H1N1 / Influenza Virus Type A, H3N2 / Influenza Virus Type B (Victoria Lineage) / Influenza Virus, Type B (Yamagata Lineage)
J07BBOI	Vaccines	Influenza Virus (Whole Virion, Inactivated), Containing Antigen Of: A/Vietnam/1203/2004 (H5N1)
J07BC01	Vaccines	Hepatitis B Surface Antigen
J07BC20	Vaccines	Hepatitis-A Virus (Inactivated) / Hepatitis-B Surface Antigen
J07BD04	Vaccines	Virus, Live Attenuated, Measles, Virus, Live Attenuated, Mumps, Virus, Live Attenuated, Rubella, Virus, Live Attenuated, Varicella
J07BD52	Vaccines	Measles Virus Enders Edmonston Strain (Live, Attenuated) / Mumps Virus Jeryl Lynn (Level B) Strain (Live, Attenuated) / Rubella Virus Wistar Ra 27/3 Strain (Live, Attenuated)
J07BH01	Vaccines	Human Rotavirus, Live Attenuated
J07BH02	Vaccines	Rotavirus Serotype G1, Serotype G2, Serotype G3, Serotype G4, Serotype P1
J07BK02	Vaccines	Varicella-Zoster Virus (Live, Attenuated)
J07BM01	Vaccines	Human Papillomavirus Type 6 L1 Protein / Human Papillomavirus Type 11 L1 Protein / Human Papillomavirus Type 16 L1 Protein / Human Papillomavirus Type 18 L1 Protein
J07BM02	Vaccines	Human Papillomavirus1 Type 16 L1 Protein / Human Papillomavirus Type 18 L1 Protein
J07BX	Vaccines	Modified Vaccinia Ankara - Bavarian Nordic (Mva-Bn) Virus
J07CA09	Vaccines	Diphtheria Toxoid /Tetanus Toxoid / Two-Component Acellular Pertussis(Pertussis Toxoidand Filamentous Haemagglutinin) /Inactivated Poliomyelitis Virus Types 1,2 And 3 /Haemophilus Influenzae Type-B Polysaccharide (Polyribosylribitol Phosphate) Conjugated To Tetanus Protein / Hepatitis-B Surface Antigen
L01	Antineoplastic agents	Olaparib
L01AB01	Antineoplastic agents	Busulfan
L01AC01	Antineoplastic agents	Thiotepa
L01AX03	Antineoplastic agents	Temozolomide
L01BA04	Antineoplastic agents	Pemetrexed
L01BB02	Antineoplastic agents	6-Mercaptopurine Monohydrate
L01BB04	Antineoplastic agents	Cladribine
L01BB06	Antineoplastic agents	Clofarabine
L01BB07	Antineoplastic agents	Nelarabine
L01BC01	Antineoplastic agents	Cytarabine
L01BC06	Antineoplastic agents	Capecitabine
L01BC07	Antineoplastic agents	Azacitidine
L01BC08	Antineoplastic agents	Decitabine

ATC Code	Therapeutic subgroup	Chemical substance
L01BC53	Antineoplastic agents	Tegafur / Gimeracil / Oteracil
L01CA05	Antineoplastic agents	Vinflunine
L01CD	Antineoplastic agents	Cabazitaxel
L01CD01	Antineoplastic agents	Paclitaxel
L01CD02	Antineoplastic agents	Docetaxel
L01CX01	Antineoplastic agents	Trabectedin
L01DB	Antineoplastic agents	Doxorubicin Hydrochloride
L01DB01	Antineoplastic agents	Doxorubicin Hydrochloride
L01DB11	Antineoplastic agents	Pixantrone Dimaleate
L01XC	Antineoplastic agents	Ramucirumab
L01XC02	Antineoplastic agents	Rituximab
L01XC03	Antineoplastic agents	Trastuzumab
L01XC06	Antineoplastic agents	Cetuximab
L01XC07	Antineoplastic agents	Bevacizumab
L01XC08	Antineoplastic agents	Panitumumab
L01XC09	Antineoplastic agents	Catumaxomab
L01XC10	Antineoplastic agents	Ofatumumab
L01XC11	Antineoplastic agents	Ipilimumab
L01XC12	Antineoplastic agents	Brentuximab Vedotin
L01XC13	Antineoplastic agents	Pertuzumab
L01XC14	Antineoplastic agents	Trastuzumab Emtansine
L01XC15	Antineoplastic agents	Obinutuzumab
L01XD05	Antineoplastic agents	Temoporfin
L01XE	Antineoplastic agents	Cabozantinib
L01XE01	Antineoplastic agents	Imatinib
L01XE02	Antineoplastic agents	Gefitinib
L01XE04	Antineoplastic agents	Sunitinib
L01XE05	Antineoplastic agents	Sorafenib
L01XE06	Antineoplastic agents	Dasatinib
L01XE07	Antineoplastic agents	Lapatinib
L01XE08	Antineoplastic agents	Nilotinib
L01XE09	Antineoplastic agents	Temsirolimus
L01XE10	Antineoplastic agents	Everolimus
L01XE11	Antineoplastic agents	Pazopanib
L01XE13	Antineoplastic agents	Afatinib
L01XE14	Antineoplastic agents	Bosutinib (As Monohydrate)
L01XE15	Antineoplastic agents	Vemurafenib
L01XE16	Antineoplastic agents	Crizotinib
L01XE17	Antineoplastic agents	Axitinib
L01XE18	Antineoplastic agents	Ruxolitinib (As Phosphate)
L01XE21	Antineoplastic agents	Regorafenib
L01XE23	Antineoplastic agents	Dabrafenib
L01XE24	Antineoplastic agents	Ponatinib
L01XE25	Antineoplastic agents	Trametinib

ATC Code	Therapeutic subgroup	Chemical substance
L01XE27	Antineoplastic agents	Ibrutinib
L01XE3	Antineoplastic agents	Nintedanib
L01XX05	Antineoplastic agents	Hydroxycarbamide
L01XX17	Antineoplastic agents	Topotecan
L01XX22	Antineoplastic agents	Alitretinoin
L01XX23	Antineoplastic agents	Mitotane
L01XX25	Antineoplastic agents	Bexarotene
L01XX27	Antineoplastic agents	Arsenic Trioxide
L01XX32	Antineoplastic agents	Bortezomib
L01XX34	Antineoplastic agents	Erlotinib
L01XX35	Antineoplastic agents	Anagrelide
L01XX41	Antineoplastic agents	Eribulin
L01XX43	Antineoplastic agents	Vismodegib
L01XX44	Antineoplastic agents	Aflibercept
L01XX47	Antineoplastic agents	Idelalisib
L02BA02	Endocrine therapy	Toremifene
L02BA03	Endocrine therapy	Fulvestrant
L02BX02	Endocrine therapy	Degarelix
L02BX03	Endocrine therapy	Abiraterone Acetate
L03AA02	Immunomodulating agents	Filgrastim
L03AA13	Immunomodulating agents	Pegfilgrastim
L03AA14	Immunomodulating agents	Lipegfilgrastim
L03AB05	Immunomodulating agents	Interferon Alfa-2B
L03AB07	Immunomodulating agents	Interferon Beta-1A
L03AB08	Immunomodulating agents	Interferon Beta-1B
L03AB10	Immunomodulating agents	Peginterferon Alfa-2B
L03AB11	Immunomodulating agents	Peginterferon Alfa-2A
L03AB13	Immunomodulating agents	Peginterferon Beta-1A
L03AX11	Immunomodulating agents	Tasonermin
L03AX14	Immunomodulating agents	Histamine Dihydrochloride
L03AX15	Immunomodulating agents	Mifamurtide
L03AX16	Immunomodulating agents	Plerixafor
L04AA	Immunosuppressive agents	Vedolizumab
L04AA06	Immunosuppressive agents	Mycophenolate Mofetil
L04AA10	Immunosuppressive agents	Sirolimus
L04AA13	Immunosuppressive agents	Leflunomide
L04AA14	Immunosuppressive agents	Anakinra
L04AA23	Immunosuppressive agents	Natalizumab
L04AA24	Immunosuppressive agents	Abatacept
L04AA25	Immunosuppressive agents	Eculizumab
L04AA26	Immunosuppressive agents	Belimumab
L04AA27	Immunosuppressive agents	Fingolimod Hydrochloride
L04AA28	Immunosuppressive agents	Belatacept
L04AA31	Immunosuppressive agents	Teriflunomide

ATC Code	Therapeutic subgroup	Chemical substance
L04AA32	Immunosuppressive agents	Apremilast
L04AA34	Immunosuppressive agents	Alemtuzumab
L04AB01	Immunosuppressive agents	Etanercept
L04AB02	Immunosuppressive agents	Infliximab
L04AB04	Immunosuppressive agents	Adalimumab
L04AB05	Immunosuppressive agents	Certolizumab Pegol
L04AB06	Immunosuppressive agents	Golimumab
L04AC02	Immunosuppressive agents	Basiliximab
L04AC05	Immunosuppressive agents	Ustekinumab
L04AC07	Immunosuppressive agents	Tocilizumab
L04AC08	Immunosuppressive agents	Canakinumab
L04AC10	Immunosuppressive agents	Secukinumab
L04AC11	Immunosuppressive agents	Siltuximab
L04AD02	Immunosuppressive agents	Tacrolimus
L04AX02	Immunosuppressive agents	Thalidomide
L04AX04	Immunosuppressive agents	Lenalidomide
L04AX05	Immunosuppressive agents	Pirfenidone
L04AX06	Immunosuppressive agents	Pomalidomide
M01AH04	Antiinflammatory and antirheumatic products	Parecoxib Sodium
M03AX01	Muscle relaxants	Botulinum Toxin Type B
M04AA03	Antigout preparations	Febuxostat
M04AX02	Antigout preparations	Pegloticase
M05BA06	Drugs for treatment of bone diseases	Ibandronic Acid
M05BA08	Drugs for treatment of bone diseases	Zoledronic Acid
M05BB03	Drugs for treatment of bone diseases	Alendronate Sodium Trihydrate / Colecalciferol
M05BC01	Drugs for treatment of bone diseases	Dibotermin Alfa
M05BC02	Drugs for treatment of bone diseases	Eptotermin Alfa
M05BX03	Drugs for treatment of bone diseases	Strontium Ranelate
M05BX04	Drugs for treatment of bone diseases	Denosumab
M09AB02	Other drugs for disorders of the musculo-skeletal system	Collagenase Clostridium Histolyticum
M09AX02	Other drugs for disorders of the musculo-skeletal system	Characterised Viable Autologous Cartilage Cells Expanded Ex Vivo Expressing Specific Marker Proteins
N01BB20	Anesthetics	Lidocaine / Prilocaine
N01BX04	Anesthetics	Capsaicin
N02AB03	Analgesics	Fentanyl
N02BG08	Analgesics	Ziconotide
N03AF03	Antiepileptics	Rufinamide
N03AF04	Antiepileptics	Eslicarbazepine Acetate
N03AX14	Antiepileptics	Levetiracetam
N03AX15	Antiepileptics	Zonisamide
N03AX16	Antiepileptics	Pregabalin
N03AX17	Antiepileptics	Stiripentol

ATC Code	Therapeutic subgroup	Chemical substance
N03AX18	Antiepileptics	Lacosamide
N03AX21	Antiepileptics	Retigabine
N03AX22	Antiepileptics	Perampanel
N04B	Anti-parkinson drugs	Safinamide Methanesulfonate
N04BA03	Anti-parkinson drugs	Levodopa / Carbidopa / Entacapone
N04BC05	Anti-parkinson drugs	Pramipexole Dihydrochloride Monohydrate
N04BC09	Anti-parkinson drugs	Rotigotine
N04BD02	Anti-parkinson drugs	Rasagiline
N04BX01	Anti-parkinson drugs	Tolcapone
N04BX02	Anti-parkinson drugs	Entacapone
N05AE05	Psycholeptics	Lurasidone
N05AH01	Psycholeptics	Loxapine
N05AH03	Psycholeptics	Olanzapine
N05AH05	Psycholeptics	Asenapine Maleate
N05AX12	Psycholeptics	Aripiprazole
N05AX13	Psycholeptics	Paliperidone
N05CD08	Psycholeptics	Midazolam
N05CF03	Psycholeptics	Zaleplon
N05CH01	Psycholeptics	Melatonin
N05CM18	Psycholeptics	Dexmedetomidine Hydrochloride
N06AX21	Psychoanaleptics	Duloxetine
N06AX22	Psychoanaleptics	Agomelatine
N06AX26	Psychoanaleptics	Vortioxetine
N06BC01	Psychoanaleptics	Caffeine Citrate
N06DA03	Psychoanaleptics	Rivastigmine
N06DX01	Psychoanaleptics	Memantine Hydrochloride
N07BA03	Other nervous system drugs	Varenicline
N07BB05	Other nervous system drugs	Nalmefene Hydrochloride Dihydrate
N07BC51	Other nervous system drugs	Buprenorphine / Naloxone
N07XX02	Other nervous system drugs	Riluzole
N07XX04	Other nervous system drugs	Sodium Oxybate
N07XX05	Other nervous system drugs	Amifampridine
N07XX07	Other nervous system drugs	Fampridine
N07XX08	Other nervous system drugs	Tafamidis
N07XX09	Other nervous system drugs	Dimethyl Fumarate
N07XX59	Other nervous system drugs	Dextromethorphan / Quinidine
P01BF05	Antiprotozoals	Piperaquine Tetraphosphate / Dihydroartemisinin
R01AD12	Nasal preparations	Fluticasone Furoate
R01BA52	Nasal preparations	Desloratadine / Pseudophedrine Sulphate
R03	Anti-asthmatics	Glycopyrronium Bromide / Indacaterol Maleate
R03AC18	Anti-asthmatics	Indacaterol Maleate
R03AK07	Anti-asthmatics	Budesonide / Formoterol Fumarate Dihydrate
R03AK10	Anti-asthmatics	Fluticasone Furoate / Vilanterol

ATC Code	Therapeutic subgroup	Chemical substance
R03AL	Anti-asthmatics	Aclidinium Bromide / Formoterol Fumarate Dihydrate
R03AL03	Anti-asthmatics	Umeclidinium Bromide / Vilanterol Trifenatate
R03AL04	Anti-asthmatics	Indacaterol / Glycopyrronium Bromide
R03AL05	Anti-asthmatics	Aclidinium / Formoterol Fumarate Dihydrate
R03BB	Anti-asthmatics	Aclidinium Bromide, Micronised
R03BB06	Anti-asthmatics	Glycopyrronium Bromide
R03BB07	Anti-asthmatics	Umeclidinium Bromide
R03DX05	Anti-asthmatics	Omalizumab
R03DX07	Anti-asthmatics	Roflumilast
R03DX08	Anti-asthmatics	Roflumilast
R05CB16	Cough and cold preparations	Mannitol
R06AX27	Antihistamines for systemic use	Desloratadine
R07AX	Other respiratory system products	Nitric Oxide
R07AX02	Other respiratory system products	Ivacaftor
S01	Ophthalmologicals	Brinzolamide / Brimonidine Tartrate
S01BA01	Ophthalmologicals	Dexamethasone
S01BC10	Ophthalmologicals	Nepafenac
S01BC11	Ophthalmologicals	Bromfenac Sodium Sesquihydrate
S01EC04	Ophthalmologicals	Brinzolamide
S01ED51	Ophthalmologicals	Brinzolamide / Timolol
S01EE03	Ophthalmologicals	Bimatoprost
S01EE04	Ophthalmologicals	Travoprost
S01GX06	Ophthalmologicals	Emedastine
S01GX09	Ophthalmologicals	Olopatadine Hydrochloride
S01LA01	Ophthalmologicals	Verteporfin
S01LA03	Ophthalmologicals	Pegaptanib
S01LA04	Ophthalmologicals	Ranibizumab
S01LA05	Ophthalmologicals	Aflibercept
S01XA18	Ophthalmologicals	Ciclosporin
S01XA19	Ophthalmologicals	Ex Vivo Expanded Autologous Human Corneal Epithelial Cells Containing Stem Cells
S01XA22	Ophthalmologicals	Ocriplasmin
V	Various	Copper (64Cu) Chloride
V03AB17	All other therapeutic products	Methylthioninium Chloride
V03AB33	All other therapeutic products	Hydroxocobalamin
V03AB35	All other therapeutic products	Sugammadex
V03AC02	All other therapeutic products	Deferiprone
V03AC03	All other therapeutic products	Deferasirox
V03AE02	All other therapeutic products	Sevelamer
V03AE05	All other therapeutic products	Mixture Of Polynuclear Iron(Iii)-Oxyhydroxide, Sucrose And Starches
V03AF02	All other therapeutic products	Dexrazoxane Hydrochloride
V03AF07	All other therapeutic products	Rasburicase
V03AF08	All other therapeutic products	Palifermin

ATC Code	Therapeutic subgroup	Chemical substance
V03AX03	All other therapeutic products	Cobicistat On Silicon Dioxide
V04CX	Diagnostic agents	13C-Urea
V04D	Diagnostic agents	Sulesomab
V08CA06	Contrast media	Gadoversetamide
V08DA01	Contrast media	Perflutren
V08DA04	Contrast media	Perflutren
V09	Diagnostic radiopharmaceuticals	Yttrium [90Y] Chloride
V09AB03	Diagnostic radiopharmaceuticals	Ioflupane (123L)
V09AX04	Diagnostic radiopharmaceuticals	Flutemetamol (18F)
V09AX05	Diagnostic radiopharmaceuticals	Florbetapir (18F)
V09AX06	Diagnostic radiopharmaceuticals	Florbetaben (18F)
V09HA03	Diagnostic radiopharmaceuticals	Besilesomab
V09IA09	Diagnostic radiopharmaceuticals	Tilmanocept
V10BX02	Therapeutic radiopharmaceuticals	Samarium [153Sm] Lexidronam Pentasodium
V10XX02	Therapeutic radiopharmaceuticals	Ibritumomab Tiuxetan
V10XX03	Therapeutic radiopharmaceuticals	Radium Ra223 Dichloride

APPENDIX 4

List of ATC codes covered by nationally authorised products extracted 15/06/2015

ATC Code	Therapeutic subgroup
A01	Stomatological Preparations
A02	Drugs For Acid Related Disorders
A03	Drugs For Functional Gastrointestinal Disorders
A04	Antiemetics And Antinauseants
A05	Bile And Liver Therapy
A06	Laxatives
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents
A08	Antiobesity Preparations, Excluding Diet Products
A09	Digestives, Incl Enzymes
A10	Drugs Used In Diabetes
A11	Vitamins
A12	Mineral Supplements
A13	Tonics
A15	Appetite Stimulants
A16	Other Alimentary Tract And Metabolism Products
B01	Antithrombotic Agents
B02	Antihemorrhagics
B03	Antianemic Preparations
B05	Plasma Substitutes And Perfusion Solutions
B06	Other Hematological Agents
C01	Cardiac Therapy
C02	Antihypertensives
C03	Diuretics
C04	Peripheral Vasodilators
C05	Vasoprotectives
C07	Beta Blocking Agents
C08	Calcium Channel Blockers
C09	Agents Acting On The Renin-Angiotensin System
C10	Lipid Modifying Agents
D01	Antifungals For Dermatological Use
D02	Emollients And Protectives
D03	Preparations For Treatment Of Wounds & Ulcers
D04	Antipruritics, Incl. Antihistamines, Anesthetics, Etc.
D05	Antipsoriatics
D06	Antibiotics And Chemotherapeutics For Dermatological Use
D07	Corticosteroids, Dermatological Preparations
D08	Antiseptics And Disinfectants
D09	Medicated Dressings
D10	Anti-Acne Preparations
D11	Other Dermatological Preparations
G01	Gynecological Antiinfectives And Antiseptics
G02	Other Gynecologicals
G03	Sex Hormones And Modulators Of The Genital System
G04	Urologicals

ATC Code	Therapeutic subgroup
H01	Pituitary And Hypothalamic Hormones
H02	Corticosteroids For Systemic Use
H03	Thyroid Therapy
H04	Pancreatic Hormones
H05	Calcium Homeostasis
J01	Antibacterials For Systemic Use
J02	Antimycotics For Systemic Use
J04	Antimycobacterials
J05	Antivirals For Systemic Use
J06	Immune Sera And Immunoglobulins
J07	Vaccines
L01	Antineoplastic Agents
L02	Endocrine Therapy
L03	Immunomodulating Agents
L04	Immunosuppressive Agents
M01	Antiinflammatory And Antirheumatic Products
M02	Topical Products For Joint And Muscular Pain
M03	Muscle Relaxants
M04	Antigout Preparations
M05	Drugs For Treatment Of Bone Diseases
M09	Other Drugs For Disorders Of The Musculo-Skeletal System
N01	Anesthetics
N02	Analgesics
N03	Antiepileptics
N04	Anti-Parkinson Drugs
N05	Psycholeptics
N06	Psychoanaleptics
N07	Other Nervous System Drugs
P01	Antiprotozoals
P02	Anthelmintics
P03	Ectoparasiticides, Incl. Scabicides, Insecticides And Repellents
R01	Nasal Preparations
R02	Throat Preparations
R03	Anti-Asthmatics
R05	Cough And Cold Preparations
R06	Antihistamines For Systemic Use
R07	Other Respiratory System Products
S01	Ophthalmologicals
S02	Otologicals
S03	Ophthalmological And Otological Preparations
V01	Allergens
V03	All Other Therapeutic Products
V04	Diagnostic Agents
V06	General Nutrients

ATC Code	Therapeutic subgroup
V07	All Other Non-Therapeutic Products
V08	Contrast Media
V09	Diagnostic Radiopharmaceuticals
V10	Therapeutic Radiopharmaceuticals

APPENDIX 5

List of medicines procured by the Malta National Health Service June 2015

Active ingredient	Dosage form	Strength	ATC code
Acetazolamide	Injection	500mg	S01EC01
	Tablets	250mg	S01EC01
Acetylcholine	Injection	1%	S01EB09
Acetylcysteine	Eye drops	5%	S01XA08
	Injection	200mg/mL in 10mL	V03AB23
Aciclovir	Eye Ointment	3%	S01AD03
	Tablets	200mg	J05AB01
	Tablets	800mg	J05AB01
	Cream	5%	D06BB03
	Injection	250mg	J05AB01
	Suspension	200mg/5mL	J05AB01
Acipimox	Capsules	250mg	C10AD06
Acitretin	Capsules	10mg	D05BB02
	Capsules	25mg	D05BB02
Actinomycin D	Injection	500mcg	L01DA01
Adenosine	Injection	6mg (3mg/mL)	C01EB10
Adrenaline	Injection	1:1000 in 1mL	C01CA24
	Injection	1:10000 in 10mL	C01CA24
	Prefilled Injection	1:10000 in 10mL	C01CA24
Albendazole	Tablets	400mg	P02CA03
Albumin Human	Infusion	20%	B05AA01
	Infusion	4% or 5%	B05AA01
Alcohol Dehydrated Bp	Injection		V03AB16
Alfacalcidol	Oral drops	2mcg/mL	A11CC03
	Tablets	0.25mcg	A11CC03
	Tablets	1mcg	A11CC03
Alfentanil	Injection	500mcg/mL in 10mL	N01AH02
	Injection	500mcg/mL in 2mL	N01AH02
Alginate Compound	Sachets		A02AX
Alimemazine Tartrate	Syrup	30mg/5mL	R06AD01
Allopurinol	Tablets	100mg	M04AA01
	Tablets	300mg	M04AA01
Alpha Tocopheryl	Suspension	100mg/mL	A11HA03
	Tablets	50-150mg (134mg)	A11HA03
	Tablets	670mg (1000 IU)	A11HA03
Alteplase	Injection	29 units (50mg)	B01AD02
Amantadine	Tablets	100mg	N04BB01
Amikacin	Injection	500mg in 2mL	J01GB06
Amiloride + Hydrochlorothiazide	Tablets	5mg + 50mg	C03EA01
Amino Acid With Electrolytes	Injection	18g nitrogen/L	B05BA31
	Injection	13-16g nitrogen/L	B05BA01
Aminophylline	IV Ampoules	250mg in 10mL	R03DA05

Active ingredient	Dosage form	Strength	ATC code
Amiodarone HCl	Tablets	200mg	C01BD01
	Infusion	50mg/mL in 3mL	C01BD01
Amitriptyline	Tablets	10mg	N06AA09
	Tablets	25mg	N06AA09
Amlodipine	Tablets	10mg	C08CA01
	Tablets	5mg	C08CA01
Amoxicillin	Capsules	250mg	J01CA04
	Injection	250mg	J01CA04
	Injection	500mg	J01CA04
	Sachets	3g	J01CA04
	Syrup	125mg/5mL	J01CA04
Amoxicillin + Clavulanic Acid	Syrup	156mg/5mL	J01CR02
	Injection	1g + 200mg	J01CR02
	Injection	500mg + 100mg	J01CR02
	Tablets	250mg + 125mg	J01CR02
Amphotericin	Injection	50mg	J02AA01
Amphotericin	Liposomal Infusion	50mg	J02AA01
Amsacrine	Infusion	75mg Vial	L01XX01
Anastrozole	Tablets	1mg	L02BG03
Angiotensin-Ii Receptor Antagonists	Tablets		C09CA03
Antacid	Chewable Tablets		A02AX
Anti-D [Rho] Immunoglobulin	Injection	250mcg (1250 IU)	J06BB01
Anti-Haemophiliac Factor Ix	Infusion	500IU	B02BD04
Anti-Haemophiliac Factor VIII	Infusion	500IU	B02BD02
Anti-Haemophiliac Factor VIII	Infusion	1000IU	B02BD02
Anti-Haemophiliac Factor VIII Inhibitor	Injection IV	500U or 1000U	B02BD03
Anti-Haemophiliac Factor VIII Intermediate	Injection IV	500IU	B02BD06
Anti-Human Thymocyte	Immunoglobulin		L04AA04
Anti-Rabies (Human)	Immunoglobulin		J06BB05
Aprepitant	Capsules	125mg	A04AD12
	Capsules	80mg	A04AD12
Aprotinin	Injection	10000KIU/mL	B02AB01
Aqueous Cream	Cream		D02AX

Active ingredient	Dosage form	Strength	ATC code
Argatroban	Concentrate for Solution for Infusion	100mg/L	B01AE03
Artificial Saliva	Solution		A01AD11
Ascorbic Acid	Tablets		A11GA01
Asparaginase	Injection	10000IU	L01XX02
Aspirin	Tablets	300mg	N02BA01
	Tablets	75mg	B01AC06
	Tablets Effervescent	300mg	N02BA01
	Injection	500mg	N02BA01
Atenolol	Injection	500mcg/mL in 10mL	C07AB03
	Tablets	25mg or 50mg	C07AB03
	Tablets	100mg	C07AB03
Atomoxetine	Capsules	18mg	N06BA09
	Capsules	25mg	N06BA09
	Capsules	40mg	N06BA09
Atorvastatin	Tablets 10mg		C10AA05
	Tablets 20mg		C10AA05
	Tablets 40mg		C10AA05
	Tablets 80mg		C10AA05
Atosiban	Injection IV	7.5mg/mL	G02CX01
Atracurium Besylate	Injection	10mg/mL in 2.5mL	M03AC04
Atropine Sulphate	Eye drops	1%	S01FA01
	Injection	600mcg/mL	A03BA01
	Prefilled Injection	100mcg/mL in 10mL	A03BA01
	Tablets	0.6mg	A03BA01
Atropine Sulphate + Pralidoxime Chloride	Kit - InjectionS	2mg + 600mg	V03AB04
Atropine Sulphate	Single use eye drops	1% IN 0.5mL	S01FA01
Azathioprine	Tablets	50mg	L04AX01
Azithromycin	Capsules	250mg	J01FA10
	Capsules	500mg	J01FA10
	Suspension	200mg/5mL	J01FA10
Aztreonam	Injection	1g	J01DF01
	Injection	2g	J01DF01
B.C.G. (Bacillus Calmette-Guérin)	Vaccine		J07AN01
	Intravesical Injection	81mg	L03AX03
Baclofen	Intratechal Vials		M03BX01
	Syrup	5mg/5mL	M03BX01
	Tablets	10mg	M03BX01
	Tablets	25mg	M03BX01
Basiliximab	Injection IV	20mg	L04AA09
Beclometasone Dipropionate	Inhaler	250mcg	R03BA01
	Inhaler	50mcg	R03BA01
	Nasal Spray	50mcg	R01AD01

Active ingredient	Dosage form	Strength	ATC code
Bendroflumethiazide	Tablets	2.5mg	C03AA01
	Tablets	5mg	C03AA01
Benzathine Benzylpenicillin	Injection	1.2 MU	J01CE08
Benzatropine Mesylate	Tablets	2mg	N04AC01
Benzoin	Tincture	50mL	R01AX10
Benzylpenicillin	Injection	600mg	J01CE01
Beta-Blocker Preservative Free (Timolol, Betaxolol Or Levobunolol)	Eye drops		S01ED04
Betamethasone + Clioquinol	Ointment	0.1% + 3%	D07CC01
Betamethasone Sodium Phosphate	Eye drops	0.10%	S01BA06
Betamethasone Dipropionate	Cream	0.05%	D07AC01
Betamethasone Valerate	Cream	0.10%	D07AC01
	Ointment	0.10%	D07AC01
	Scalp application	0.10%	D07AC01
	Ointment	0.025%	D07AC01
Betaxolol HCl	Eye drops	0.25% (Suspension) or 0.5% (Solution)	S01ED02
Bevacizumab	Vials	100mg/4mL	S01LA
Bexarotene	Capsules	75mg	L01XX25
Bezafibrate	Modified release Tablets	400mg	C10AB02
Bicalutamide	Tablets	50mg	L02BB03
Bisacodyl	Suppositories	10mg	A06AB02
	Tablets	5mg	A06AB02
Bismuth Subnitrate + Iodoform Paste	Impregnated gauze		D09AA
Bleomycin Sulphate	Injection	15000 IU	L01DC01
Bortezomib	Vials	1mg	L01XX32
Botulinum A Toxin Haemagglutinin Complex	Injection SC	100IU	M03AX01
Botulism Antitoxin Type A, B And E Immunoglobulin	Injection		J06AA04
Bowel Cleansing Prep (Adult)	Powder		A06A
Bowel Cleansing Prep (Paediatric)	Powder		A06A
Brimonidine Tartrate	Eye drops	0.20%	S01EA05
Bromazepam	Tablets	1.5mg	N05BA08
	Tablets	3mg	N05BA08
	Tablets	6mg	N05BA08
Bromhexine	Syrup	8mg/10mL	R05CB02

Active ingredient	Dosage form	Strength	ATC code
Bromocriptine Mesylate	Tablets	2.5mg	G02CB01
Budesonide	Breath-Actuated metered dose Powder Inhaler	100mcg/dose	R03BA02
	Controlled release Capsules	3mg	A07EA06
	Enema	2mg/100mL	A07EA
	Inhaler	200mcg/dose	R03BA02
	Inhaler	50mcg/dose	R03BA02
	Nebulise Solution Ampoules	0.25mg/mL	R03BA02
	Nebuliser Solution Ampoules	0.5mg/mL	R03BA02
Bumetanide	Injection	0.5mg/mL in 4mL	C03CA02
	Tablets	1mg	C03CA02
	Tablets	5mg	C03CA02
Bupivacaine	Injection	0.25%	N01BB01
	Injection	0.50%	N01BB01
Bupivacaine + Glucose	Injection	5mg + 80mg/mL in 4mL	N01BB51
Bupivacaine + Adrenaline	Injection	5mg + 1:200000 in 10mL	N01BB51
	Injection	2.5mg + 1:200000 in 10mL	N01BB51
Buspirone Hydrochloride	Tablets	10mg	N05BE01
Busulfan	Tablets	2mg	L01AB01
C1 Esterase Inhibitor	Vials	500IU/10mL	B02AB03
Cabergoline	Tablets	0.5mg	G02CB03
Caffeine Citrate	Powder/Oral Liquid		N06BC01
Calcipotriol	Ointment	50mcg/g	D05AX02
Calcipotriol + Betametasone	Ointment	50mcg + 0.05%/g	D05AX52
Calcitonin (Salmon Synthetic)	Injection	100IU/mL in 1mL	H05BA01
Calcium	Tablets Effervescent	400-500mg	A12AA04
Calcium Carbonate	Chewable Tablets	1500mg	A02AC01
Calcium Chloride	Injection IV		A12AA07
	Prefilled Injection		A12AA07
Calcium Folinate (Calcium Leucovorin/Folinic Acid)	Injection	50mg/5mL	V03AF03
	Tablets	15mg	V03AF03
Calcium Gluconate	Injection	100mg/mL in10mL	A12AA03
Calcium Hydroxide	Powder	90%	V03AX
Calcium Lactate	Tablets	300mg	A12AA05
Calcium Polystyrene Sulphonate (Calcium Resonium)	Powder		V03AE01

Active ingredient	Dosage form	Strength	ATC code
Captopril	Tablets	25mg	C09AA01
Captopril	Tablets	50mg	C09AA01
Carbamazepine	Controlled release Tablets	200mg	N03AF01
	Controlled release Tablets	400mg	N03AF01
	Syrup	100mg/5mL	N03AF01
	Tablets	200mg	N03AF01
Carbidopa + Levodopa	Tablets	25mg + 250mg	N04BA02
	Tablets	10mg + 100mg	N04BA02
Carbidopa + Levodopa + Entacapone	Tablets	25mg + 100mg + 200mg	N04B
Carbimazole	Tablets	5mg	H03BB01
Carbonic Anhydrase Inhibitors	Eye drops		S01EC03
Carboplatin	Injection	150mg in 15mL	L01XA02
Carboprost	Injection	250mcg/mL	G02ADD4
Cardioplegia	Concentrate		B05XA16
Carvedilol	Tablets	6.25mg	C07AG02
	Tablets	25mg	C07AG02
Cefalexin	Capsules	250mg	J01DB01
	Syrup	125mg/5mL	J01DB01
Cefepime Dihydrochloride Monohydrate	Injection	1g	J01DE01
Cefotaxime Sodium	Injection	1g	J01DD01
Ceftazidime Pentahydrate	Injection	1g	J01DD02
Ceftriaxone Sodium	Injection IV	2g	J01DD04
	Injection IV	500mg	J01DD04
	Injection IM & IV	1g	J01DD04
Cefuroxime Sodium	Injection	250mg	J01DC02
Cefuroxime Axetil	Suspension	125mg/5mL	J01DC02
	Tablets	250mg	J01DC02
Cefuroxime Sodium	Injection	750mg	J01DC02
Charcoal Activated	Powder		A07BA01
Chloral Hydrate	Mixture		N05CC01
Chlorambucil	Tablets	2mg	L01AA02
Chloramphenicol	Capsules	250mg	J01BA01
	Eye drops	0.50%	S01AA01
	Eye ointment	1%	S01AA01
Chloramphenicol Sodium Succinate	Injection	1g	J01BA01
Chlorhexidine	Aqueous Solution		D08AC02
	Saponaceous	4%	D08AC02

Active ingredient	Dosage form	Strength	ATC code
Chlorhexidine + Cetrimide	Sachets	25mL	D08AC52
Chlorhexidine + Neomycin	Nasal Cream	0.1% + 0.5%	D08AC52
Chlorhexidine Acetate	Solution	0.05%	D08AC02
Chlorhexidine Gluconate	Mouthwash	0.20%	A01AB03
	Solution		D08AC52
	Obstetric Cream	1%	G01AX
	Obstetric Solution	5%	G01AX
Chlorhexidine Gluconate + Cetrimide	Powder	0.015% + 0.15%	D08AC52
Chloroform Water	Solution		N01AB02
Chloroquine	Syrup	150mg base/5mL	P01BA01
	Syrup	50mg/5mL	P01BA01
	Tablets	250mg	P01BA01
Chlorphenamine Maleate	Vials	10mg/mL	R06AB04
Chlorpromazine HCl	Injection	50mg	N05AA01
	Tablets	100mg	N05AA01
	Tablets	25mg	N05AA01
Cholera	Oral Vaccine		J07AE
Chorionic Gonadotrophin Human (Hcg)	Injection	1500 IU	G03GA01
	Injection	5000 IU	G03GA01
Ciclosporin	Capsules	100mg	L04AD01
	Capsules	25mg	L04AD01
	Oral Solution	100mg/mL	L04AD01
	Injection IV	50mg in 1 ml	L04AD01
Ciprofloxacin	Injection IV	200mg/100mL	J01MA02
	Injection IV	100mg/50mL	J01MA02
	Suspension	250mg/5mL	J01MA02
	Tablets	250mg	J01MA02
Cisplatin	Injection	10mg	L01XA01
	Injection	50mg	L01XA01
Cladribine	Injection	10mg	L01BB04
Clarithromycin	Injection IV	500mg	J01FA09
	Syrup	125mg/5mL	J01FA09
	Tablets	250mg	J01FA09
Clindamycin	Capsules	150mg	J01FF01
Clindamycin Phosphate	Injection	150mg/mL in 2mL or 4mL	J01FF01
Clobazam	Tablets	10mg	N05BA09
Clobetasol Propionate	Scalp application	0.05%	D07AD01
	Cream	0.05%	D07AD01
	Ointment	0.05%	D07AD01
Clodronate	Capsules	400mg	M05BA02
Clofazimine	Tablets	100mg	J04BA01
Clomifene Citrate	Tablets	50mg	G03GB02
Clomipramine Hydrochloride	Tablets	10mg	N06AA04
	Tablets	25mg	N06AA04

Active ingredient	Dosage form	Strength	ATC code
Clonazepam	Injection	1mg/mL in 1mL	N03AE01
	Tablets	0.5mg	N03AE01
	Tablets	2mg	N03AE01
Clonidine Hydrochloride	Injection	150mcg/mL in 1mL	C02AC01
	Tablets	100mcg	C02AC01
Clopidogrel	Tablets	75mg	B01AC04
Clotrimazole	Cream	1%	D01AC01
Clotrimazole	Pessaries	100mg	G01AF02
Clozapine	Tablets	25mg	N05AH02
	Tablets	100mg	N05AH02
Coal Tar	Shampoo		D05AA
Co-Danthramer	Suspension	75/1000 in 5mL	A06AB53
Codeine Phosphate	Suspension	15mg/5mL	R05DA04
	Tablets	30mg	R05DA04
Colchicine	Tablets	500mcg	M04AC01
Colestyramine	Powder		C10AC01
Colistimethate Sodium	Injection	1 MU	J01XB01
Compound Sodium Lactate	Infusion	500mL	B05BB01
Compound Sodium Lactate	Infusion	1000mL	B05BB01
Conjugated Estrogens	Tablets	0.625mg	G03CA57
	Cream	625mcg/g	G03CA57
	Tablets	1.25mg	G03CA57
Co-Trimoxazole	Injection	480mg/5mL	J01EE01
	Syrup	240mg/5mL	J01EE01
	Syrup	480mg/5mL	J01EE01
	Tablets	400mg + 80mg	J01EE01
Cox-2 Selective Inhibitor	Tablets		M01AC06
Crotamiton	Cream	10%	D04AX
Cyclizine	Ampoules	50mg/mL	R06AE03
	Tablets	50mg	R06AE03
Cyclopentolate HCl	Eye drops	1%	S01FA04
Cyclophosphamide	Injection	500mg Vial	L01AA01
	Tablets	50mg	L01AA01
Cycloserine	Tablets	250mg	J04AB01
Cyproterone Acetate	Tablets	50mg	G03HA01
Cytarabine	Injection	100mg in 5mL	L01BC01
	Injection	500mg in 10mL	L01BC01
Dacarbazine	Injection	200mg	L01AX04
Danaparoid	Injection	750units/0.6mL	B01AB09
Dantrolene Sodium	Capsules	25mg	M03CA01
	Injection	20mg	M03CA

Active ingredient	Dosage form	Strength	ATC code
Dapsone	Tablets	100mg	J04BA02
	Tablets	50mg	J04BA02
Daptomycin	Injection	500mg	J01XX09
Daunorubicin	Liposomal Infusion	2mg/mL	L01DB02
Daunorubicin HCl	Injection	20mg	L01DB02
Deferasirox	Dispersible Tablets	250mg	V03AC03
	Dispersible Tablets	500mg	V03AC03
Demeclocycline Hydrochloride	Capsules	150mg	J01AA01
Desferrioxamine Mesilate	Injection	500mg	V03AC01
Desflurane	Inhalation anaesthetic		N01AB07
Desmopressin	Injection	4mcg/mL	H01BA02
	Intranasal Solution	100mcg/mL	H01BA02
	Nasal Spray	10mcg	H01BA02
	Tablets	0.1mg	H01BA02
Dexamethasone	Eye drops	0.10%	S01BA01
	Tablets	0.5mg	H02AB02
	Tablets	2mg	H02AB02
Dexamethasone Phosphate	Injection	4mg/mL in 2mL	H02AB02
Dexamfetamine Sulphate	Tablets	5mg	N06BA02
Dextran 40 In Dextrose	Infusion IV	10% + 5%	B05AA05
Dextrose	Infusion IV	20% in 500mL	B05BA03
	Infusion IV	5% in 100mL, 500mL and 1000mL	B05BA03
	Infusion IV	50% in 20mL and 500mL	B05BA03
Dextrose + Sodium Chloride	Injection	10% + 0.18% in 500mL	B05BB02
	Injection IV	5% + 0.225% in 500mL	B05BB02
	Injection IV	5% + 0.9% in 500mL	B05BB02
	Injection IV	10% + 0.225% in 500mL	B05BB02
	Injection IV	5% + 0.45% in 500mL	B05BB02
Dextrose Monohydrate	Infusion	10% in 500mL	B05BA03
Diamorphine Hydrochloride (Heroin)	Injection	5mg	N02AA09
	Injection	100mg	N02AA09
Diazepam	Injection	5mg/mL in 2mL	N05BA01
	Injection	10mg/2mL	N05BA01
	Rectal Tubes	10mg/2.5mL	N05BA01
	Rectal Tubes	5mg/2.5mL	N05BA01
	Syrup	2mg/5mL	N05BA01
	Tablets	5mg	N05BA01
	Tablets	2mg	N05BA01

Active ingredient	Dosage form	Strength	ATC code
Diclofenac Sodium	Eye drops	0.10%	S01BC03
	Injection	75mg	M01AB05
	Suppositories	12.5mg	M01AB05
	Tablets	25mg	M01AB05
	Suppositories	100mg	M01AB05
Dicobalt Edetate	Injection	300mg	V03AB03
Didanosine	Tablets Eneteric-Vaginal	125mg	J05AF02
	Tablets Eneteric-Vaginal	250mg	J05AF02
Diethylstilbestrol	Tablets	1mg	G03CB02, L02AA01
Digoxin	Oral Solution	0.05mg/mL	C01AA05
	Injection	500mcg/mL in 2mL	C01AA05
	Injection	250mcg/mL in 2mL	C01AA05
	Tablets	0.0625mg	C01AA05
	Tablets	0.25mg	C01AA05
Digoxin Antibodies	Injection	38mg	V03AB24
Dihydrocodeine Tartrate	Tablets	30mg	N02AA08
Diltiazem	Tablets	60mg	C08DB01
Dimercaprol	Injection	100mg (50mg/mL in 2mL)	V03AB09
Dimethyl Fumarate	Gastr-resistant Hard Capsules	120mg	N07XX09
	Gastr-resistant Hard Capsules	240mg	N07XX10
Dinoprostone	Vaginal Gel	400mcg/mL	G02AD02
	Vaginal Gel	800mcg/mL	G02AD02
	Vaginal delivery system	10mg	G02AD02
	Injection	0.75mg/0.75mL	G02AD02
Diphenhydramine Citrate + Menthol	Syrup	125mL	R05X
Diphtheria (Low Dose) + Tetanus + Polio	Vaccine		J07CA01
Diphtheria + Tetanus + Pertussis (Acellular) + Poliomyelitis (Inactivated) + Haemophilus	Vaccine		J07CA06
Dipivefrine HCl	Eye drops	0.10%	S01EA02
Dipyridamole	Injection	5mg/mL in 2mL	B01AC07
	Tablets	100mg	B01AC07
	Tablets	25mg	B01AC07
Disodium Pamidronate	Injection	15mg	M05BA03
Disopyramide	Tablets	100mg	C01BA03
Disulfiram	Tablets	200mg	N07BB01
Dobutamine	Injection	250mg	C01CA07
Docetaxel	Injection	20mg	L01CD02
	Injection	80mg	L01CD02

Active ingredient	Dosage form	Strength	ATC code
Docusate Sodium	Tablets	100mg	A06AA02
Domperidone	Suppositories	30mg	A03FA03
	Suspension	1mg/mL	A03FA03
	Tablets	10mg	A03FA03
Donepezil Hydrochloride	Tablets	5mg	N06DA02
	Tablets	10mg	N06DA02
Dopamine	Ampoules	40mg/mL in 5mL	C01CA04
Dornase Alfa	Nebuliser Solution	1000units/mL (2.5mg)	R05CB13
Doxapram	Injection	100mg	R07AB01
Doxazosin	Tablets	2mg	C02CA04
	Tablets	4mg	C02CA04
	Tablets	1mg	C02CA04
Doxorubicin HCl	Injection	10mg	L01DB01
	Injection	50mg	L01DB01
Doxycycline	Capsules	100mg	J01AA02
	Injection IV	100mg	J01AA02
Dydrogesterone	Tablets	10mg	G03DB01
Econazole	Pessaries	150mg	G01AF05
Edrophonium	Injection		N07AA
Efavirenz	Capsules	200mg	J05AG03
	Tablets	600mg	J05AG03
Enalapril	Tablets	20mg	C09AA02
	Tablets	5mg	C09AA02
Enoxaparin Sodium	Vials for Injection	100mg	B01AB05
	Vials for Injection	40mg	B01AB05
	Vials for Injection	20mg	B01AB05
	Vials for Injection	60mg	B01AB05
	Vials for Injection	80mg	B01AB05
Enoximone	Injection	100mg/20mL	C01CE03
Ephedrine	Injection	30mg	R03CA02
Epirubicin Hydrochloride	Injection	10mg	L01DB03
	Injection	50mg	L01DB03
Eptacog Alfa	Vials		B02BD08
Erlotinib	Tablets	150mg	L01XE03
Ertapenem	Powder FOR Solution FOR Infusion	1g	J01DH03
Erythromycin	Syrup	125mg/5mL	J01FA01
	Capsules/ Tablets	250mg	J01FA01
	Injection	1g	J01FA01
Esmolol HCl	Injection	10mg/mL in 250mL	C07AB09
	Vials	10mg per mL in 10mL Vials	C07AB09
Estradiol Valerate	Tablets	1mg	G03CA03
Estradiol Valerate + Norgestrel	Tablets	2mg + 0.5mg	G03FA10
Etamsylate	Injection	1g	B02BX01
Etanercept	Injection	25mg	L04AB01
	Injection	50mg	L04AB01
Ethambutol	Tablets	100mg	J04AK02
	Tablets	400mg	J04AK02

Active ingredient	Dosage form	Strength	ATC code
Ethinylestradiol	Tablets	10mcg	G03CA01
Ethionamide	Tablets	250mg	J04AD03
Ethosuximide	Syrup	250mg/5mL	N03AD01
	Capsules	250mg	N03AD01
Ethyl Chloride	Spray	100mL	N01BX01
Etomidate	Injection	20mg	N01AX07
Etoposide	Capsules	50mg	L01CB01
	Injection	100mg	L01CB01
Exemestane	Tablets	25mg	L02BG06
Factor Xiii Concentrate	Vials		B02BD07
Fenofibrate	Capsules	300mg Capsules or 200mg Capsules or 145mg Tablets	C10AB05
	Capsules	100mg or 67mg	C10AB05
Fentanyl	Injection	0.1mg/2mL	N01AH01
	Injection	0.5mg/10mL	N01AH01
	Transdermal Patches	50mcg	N02AB03
	Transdermal Patches	25mcg	N02AB03
Ferric Hydroxide Sucrose	Injection	100mg	B03AB04
Ferric Sub-Sulphate	Solution		B03AB
Fibrinogen Concentrate	Vials		B02BB01
Filgrastim	Injection	30 MIU	L03AA02
Finasteride	Tablets	5mg	G04CB01
Fingolimod	Capsules	0.5mg	L04AA27
Flavoxate	Tablets	200mg	G04B002
Flecainide Acetate	Injection	150mg/15mL	C01BC04
	Tablets	100mg	C01BC04
Flucloxacillin	Capsules	250mg	J01CF05
	Injection	250mg	J01CF05
	Injection	1000mg	J01CF05
	Syrup	125mg/5mL	J01CF05
Fluconazole	Capsules	150mg	J02AC01
	Capsules	50mg	J02AC01
	Injection	2mg/mL in 100mL	J02AC01
	Suspension	50mg/5mL	J02AC01
Fludarabine	Capsules	10mg	L01BB05
	Injection	50mg in 2mL	L01BB05
Fludrocortisone Acetate	Tablets	0.1mg	H02AA02
Fludroxycortide	Tape		D07AC07
Flumazenil	Injection	500mcg	V03AB25
Fluorescein Sodium	Injection	100mg/mL	S01JA01
Fluoromethalone	Eye drops	0.10%	S01BA07
Fluorouracil	Cream	5%	L01BC02
	Injection	500mg/10mL	L01BC02
Fluoxetine	Tablets	20mg	N06AB03
Flupentixol Decanoate	Injection	100mg/mL	N05AF01
	Injection	20mg/mL	N05AF01
Flupentixol Dihydrochloride	Tablets	0.5mg	N05AF01

Active ingredient	Dosage form	Strength	ATC code
Fluphenazine Decanoate	Injection	100mg	N05AB02
	Injection	25mg	N05AB02
Flutamide	Tablets	250mg	L02BB01
Fluticasone	Inhaler	250mcg	R03BA05
	Inhaler	50mcg	R03BA05
Fluvastatin	Capsules	40mg	C10AA04
	Prolonged release Tablets	80mg	C10AA04
Fluvoxamine Maleate	Tablets	100mg	N06AB08
Folic Acid	Oral Solution	2.5mg/5mL	B03BB01
	Tablets	5mg	B03BB01
Formaldehyde	Solution	5L	D08AX
Foscarnet	Injection IV	24mg/mL	J05AD01
Framycetin + Dexamethasone + Gramicidin	Eye/Ear drops	0.5% + 0.05% + 0.005%	S02CA06
Furosemide + Amiloride	Tablets	40mg + 5mg	C03EB01
Furosemide	Injection	250mg/25mL	C03CA01
	Injection	20mg/2mL	C03CA01
	Syrup	1mg/mL	C03CA01
	Tablets	40mg	C03CA01
Fusidate Sodium	Tablets	250mg	J01XC01
Fusidic Acid	Eye drops	1%	S01AA13
	Oral Suspension	250mg/5mL	J01XC01
Gabapentin	Tablets	100mg	N03AX12
	Tablets	300mg	N03AX12
Gadofosveset Trisodium	Injection	244mg/mL	V08CA11
Ganciclovir	Injection	500mg	J05AB06
Gemcitabine Hydrochloride	Injection	1g	L01BC05
Gentamicin	Bead Chain	30	J01GB
	Eye/ear drops	0.30%	S03AA06
	Injection	80mg	J01GB03
	Powder		D06AX07
Gentamicin + Hydrocortisone	Ear drops	0.3% + 1%	S02AA14
Glibenclamide	Tablets	5mg	A10BB01
Gliclazide	Tablets	80mg	A10BB09
Glucagon	Injection	1mg	H04AA01
Glucose	Beverage	30%	V06DC01
	Dialysis Solution		B05CX01
	Sachets		V06DC01
Glutaraldehyde	Solution		D08AX
Glycerin	Enema	80% w/v	A06AG04
	Liquid		A06AX01
Glycerol/Glycerin	Suppositories	4g	A06AX01
Glycerol/Glycerin	Suppositories	1g	A06AX01
Glyceryl Trinitrate	Injection	1mg/mL in 50mL	C01DA02
	Metered dose Spray	400mcg	C01DA02
	Transdermal Patches	10mg/24hrs	C01DA02
	Sublingual Tablets	500mcg	C01DA02
	Transdermal Patches	5mg/24hrs	C01DA02

Active ingredient	Dosage form	Strength	ATC code
Glycine	Irrigation Solution	1.5% w/v in 3L	B05CX03
Glycopyrolate	Injection	0.6mg	A03AB02
Gonadorelin	Injection	100mcg	H01CA01
Goserelin	Implants	10.8mg	L02AE03
	Implants	3.6mg	L02AE03
Griseofulvin	Tablets	125mg	D01BA01
Growth Hormone Recombinant (Somatropin)	Injection		H01AC01
Guanethidine	Injection	10mg	C02CC02
Haemophilus Influenzae Type B	Vaccine	10mcg/0.5mL	J07AG01
Haloperidol	Capsules	0.5mg	N05AD01
	Injection	5mg	N05AD01
	Oral Solution	2mg/mL	N05AD01
	Tablets	1.5mg	N05AD01
	Tablets	5mg	N05AD01
	Injection	100mg	N05AD01
	Injection	50mg	N05AD01
Heparin Sodium	Injection	1000 IU/mL in 20mL	B01AB01
	Injection	5000 IU/mL in 5mL	B01AB01
	Infusion	500 IU in 500mL	B01AB01
	Injection	10 IU/mL IN 5mL	B01AB01
Hepatitis A	Vaccine		J07BC02
Hepatitis B	Immunoglobulin		J06BB04
Hepatitis B (Adult) (Stand- By)	Vaccine Surface Antigen		J07BC01
Hepatitis B (Paediatric) (Stand-By)	Vaccine Surface Antigen		J07BC01
Human Papillomavirus (Hpv)	Vaccine		J07BM
Hyaluronidase	Injection	1500 IU	B06AA03
Hydralazine	Injection	20mg	C02DB02
	Tablets	25mg	C02DB02
Hydrocortisone	Cream	1%	D07AA02
	Foam Enema	10%	A07EA02
	Ointment	1%	D07AA02
	Tablets	5mg or 10mg	H02AB09
	Tablets	20mg	H02AB09
Hydrocortisone + Polymyxin B + Neomycin	Ear drops	10,000 IU + 3400 IU + 10mg/mL in 5mL	S02CA03
Hydrocortisone + Urea (+/- Lactic Acid)	Cream	(1% + 10%)	D07XA01
Hydrocortisone Butyrate	Cream	0.10%	D07AB02
	Cream fatty base		D07AB02
Hydrocortisone Sodium Succinate	Injection	100mg	H02AB09
Hydrogen Peroxide	Solution	6%	A01AB02/ D08AX01

Active ingredient	Dosage form	Strength	ATC code
Hydroxocobalamin (Vitamin B12)	Injection	1mg/mL in 1mL	B03BA03
	Injection	5g	V03AB33
Hydroxycarbamide	Capsules	500mg	L01XX05
Hydroxychloroquine	Tablets	200mg	P01BA02
Hydroxyzine HCl	Tablets	25mg	N05BB01
Hyoscine Butylbromide	Injection	20mg	A03BB01
	Tablets	10mg	A03BB01
Hyoscine Hydrobromide	Injection	400mcg	A04AD01, N05CM05
Hypromellose	Eye drops	0.30%	S01KA02
Ibuprofen	Oral Suspension	100mg/5mL	M01AE01
	Tablets	200mg	M01AE01
	Injection	10mg/mL	C10EB16
Ifosfamide	Injection	2g	L01AA06
Iloprost With Trometamol	Infusion	20mcg/ml	B01AC11
Imatinib	Capsules	100mg	L01XE01
Imipenem + Cilastatin	Injection	500mg + 500mg	J01DH51
Imipramine	Tablets	10mg	N06AA02
	Tablets	25mg	N06AA02
Immunoglobulin Normal (Gammaglobulin) Iv	Injection	2.5-3g	J06BA02
	Injection	5-6g	J06BA02
Immunoglobulin Normal Im	Injection	250mg	J06BA02
Indocyanine Green	Injection	5mg/mL	V04CX
Indometacin	Capsules	25mg	M01AB01
Infliximab	Injection	100mg	L04AA12
Influenza	Vaccine		J07BB01
Insulin Aspart	Cartridges	100 units/mL in 3mL	A10AB05
Insulin Biphasic Isophane (Isophane + Neutral)	Cartridges	(70%, 30%) 100IU/mL	A10AD01
	Injection	100 IU/mL	A10AD01
Insulin Glargine	Cartridges	100 IU/mL	A10AE04
Insulin Isophane	Cartridges	100 units/mL in 3mL	A10AC01
	Injection	100 IU/mL in 10mL	A10AC01
Insulin Neutral (Soluble Insulin)	Cartridges	100 units/mL in 3mL	A10AB01
	Injection SC	100 IU/mL in 10mL	A10AB01
Interferon Alfa 2B	Injection	30 MIU	L03AB05
Interferon Beta 1B	Injection	9.6 M IU	L03AB08
Interferon Beta 1A	Injection	30mcg (6 M.I.U.)	L03AB07
Interferon Gamma	Injection	100mcg	L03AB03
Iodine Weak Solution	Solution		D08AG03
Iodixanol	Vials	320mg I/ml in 50ml or 100ml	V08AB09
Ipratropium	Inhaler	20mcg/dose	R03BB01
	Nebuliser Solution	250mcg/mL	R03BB01
Irinotecan	Vials		L01XX19
Iron + Folic Acid	Tablets/ Capsules		B03AD02

Active ingredient	Dosage form	Strength	ATC code
Isoflurane	Inhalation anaesthetic		N01AB06
Isoniazid	Tablets	100mg	J04AC01
	Injection IM	50mg/2mL	J04AC01
Isoprenaline	Injection	200mcg in 1mL	C01CA02
Isoprenaline HCl	Injection	1mg/mL in 1mL	C01CA02
	Injection	1mg/mL in 2mL	C01CA02
	Injection	5mg/mL in 5mL	C01CA02
Isopropyl Alcohol	Gel		D08AX05
	Hand rub		D08AX05
Isosorbide Dinitrate	Injection	1mg/mL in 10mL	C01DA08
	Tablets	10mg	C01DA08
Isosorbide Mononitrate	Tablets	20mg	C01DA14
	Tablets SR	60mg	C01DA14
Isotretinoin	Capsules	20mg	D10BA01
Ispaghula Husk	Powder		A06AC01
Itraconazole	Capsules	100mg	J02AC02
	Syrup	10mg/mL	J02AC02
Ivermectin	Tablets	3mg	P02CF01
Ketamine	Injection	10mg/mL in 20mL	N01AX03
	Injection	50mg/mL in 10mL	N01AX03
Labetolol HCl	Injection	5mg/mL in 20mL	C07AG01
	Tablets	100mg	C07AG01
	Tablets	200mg	C07AG01
Lactulose	Syrup	3.35g/5mL	A06AD11
Lamivudine	Oral Solution	10mg/mL	J05AF05
	Tablets	100mg	J05AF05
	Tablets	150mg	J05AF05
Lamotrigine	Dispersible Tablets	25mg	N03AX09
	Dispersible Tablets	5mg	N03AX09
	Tablets	100mg	N03AX09
	Tablets	25mg	N03AX09
	Tablets	50mg	N03AX09
Lanthanum	Chewable Tablets	750mg	V03AE03
Leflunomide	Tablets	10mg, 20mg	L04AA13
Lenalidomide	Capsules	25mg	L04AX04
Letrozole	Tablets	2.5mg	L02BG04
Leuprorelin	Injection	3.75mg	L02AE02
Levetiracetam	Syrup	100mg/mL	N03AX14
	Tablets	500mg	N03AX14
	Tablets	1000mg	N03AX14
	Concentrate for Solution for Infusion	500mg/5mL	N03AX14
Levodopa + Benserazide HCl	Disperable Tablets	100mg + 25mg	N04BA02
	Tablets	100mg + 25mg	N04BA02
	Tablets	50mg + 12.5mg	N04BA02
	Tablets	200mg + 50mg	N04BA02
Levofloxacin	Injection IV	500mg	J01MA12
	Tablets	500mg	J01MA12
Levomepromazine	Injection	25mg/mL	N05AA02
	Tablets	25mg	N05AA02

Active ingredient	Dosage form	Strength	ATC code
Levothyroxine	Tablets	100mcg	H03AA01
	Tablets	50mcg	H03AA01
Lidocaine HCl + Adrenaline	Dental Cartridges	2%	N01BB52
	Injection	2% + 1:200,000	N01BB52
	Injection	1% + 1:200,000	N01BB52
Lidocaine HCl + Prilocaine	Cream	25mg + 25mg (5%)	N01BB52, N01BB54
Lidocaine HCl	Spray	10%	D04AB01
	Injection	1%	N01BB02
	Injection	2% in 5mL	N01BB02
	Injection	4%	N01BB02
	Gel	2%	D04AB01
	Injection	2% in 20mL	N01BB02
	Prefilled Syringes	100mg/5mL	C01BB01
	Solution	4%	N01BB02
	Injection	0.2% in 5%	C01BB01
Linezolid	Tablets	600mg	J01XX08
	Vials	600mg	J01XX08
Liothyronine Sodium	Injection	20mcg	H03AA02
	Tablets	25mcg	H03AA02
Liquid Paraffin + Lanolin	Liquid	91.7% + 1.3%	A06AA51
Lisinopril	Tablets	10mg	C09AA03
Lisinopril	Tablets	5mg	C09AA03
Lithium Carbonate	Tablets	400mg	N05AN01
Lithium Citrate	Syrup	520mg/5mL	N05AN01
Lomustine	Capsules	40mg	L01AD02
Long Acting Beta2- Agonist For Patients Over 12 Years	Inhaler		R03AC12/ R03AC13
Loperamide HCl	Capsules	2mg	A07DA03
Lopinavir + Ritonavir	Oral Solution	80mg + 20mg per mL	J05AR10
	Tablets	200mg + 50mg	J05AR10
Lorazepam	Injection IM & IV	4mg/mL	N05BA06
	Tablets	1mg	N05BA06
	Tablets	2mg	N05BA06
Magnesium Sulphate	Injection	20%	B05XA05
	Paste		D11AX05
Magnesium Glycerophosphate	Tablets	97.2mg (4mmol)	A12CC
Magnesium Hydroxide + Aluminium Hydroxide + Simeticone	Oral Liquid		A02AX
Magnesium Hydroxide Mixture	Oral Liquid		A02AA04
Magnesium Sulphate	Injection	50% in 10mL	B05XA05
Malathion	Liquid	0.5% w/w	P03AX03
Mannitol	IV Infusion	10%	B05BC01
	IV Infusion	15%	B05BC01
Maprotiline HCl	Tablets	25mg	N06AA21
Maraviroc	Tablets	300mg	J05AX09
Measles + Mumps + Rubella (MMR)	Vaccine		J07BX

Active ingredient	Dosage form	Strength	ATC code
Mebendazole	Suspension	2%	P02CA01
	Tablets (Chewable)	100mg	P02CA01
Mebeverine HCl	Tablets	135mg	A03AA04
Medical Air	Gas		V03AN
Medical Oxygen 0.55m^3	Gas		V03AN01
Medical Oxygen 1.5m^3	Gas		V03AN01
Medical Oxygen 7m^3	Gas		V03AN01
Medroxyprogesterone Acetate	Tablets	100mg	L02AB02
	Tablets	5mg	G03AC06, L02AB02
Mefenamic Acid	Tablets	250mg	M01AG01
Mefloquine	Tablets	250mg	P01BC02
Melphalan	Tablets	2mg	L01AA03
Menadiol Sodium Phosphate	Tablets	10mg	B02BA02
Meningitis	Vaccine		J07AH
Mepacrine HCl	Tablets	100mg	P01AX05
Mercaptopurine	Tablets	50mg	L01BB02
Meropenem	Injection	1g	J01DH02
	Injection	500mg	J01DH02
Mesalazine	Enema	1g	A07EC02
	Suppositories	500mg	A07EC02
	Tablets	400mg	A07EC02
	Slow release Tablets	500mg	A07EC02
Mesna	Injection	100mg/mL in 10mL	V03AF01
Metformin HCl	Tablets	500mg	A10BA02
Methadone HCl	Tablets	5mg	N07AC52
	Syrup	500mL	N07BC02
Methionine	Tablets	500mg	V03AB26
Methotrexate	Tablets	2.5mg	L01BA01, L04AX03
	Vials	1000mg	L01BA01
	Vials	50mg	L01BA01
	Vials	5mg	L01BA01
Methoxsalen	Lotion	1%	D05AD02
	Tablets	10mg	D05BA02
Methylcellulose	Syrup	2%	A06AC06
Methyldopa	Tablets	250mg	C02AB
Methylphenidate HCl	Tablets	10mg	N06BA04
Methylprednisolone	Tablets	4mg	H02AB04
	Injection IM & IV	40mg	H02AB04
	Injection	500mg	H02AB04
	Injection IM	40mg/ml	H02AB04
Methylthioninium Chloride	Injection		V03AB17
Metoclopramide	Ampoules	10mg/2mL	A03FA01
	Tablets	10mg	A03FA01
Metolazone Tartrate	Tablets	5mg	C03BA08
Metoprolol Tartrate	Injection	1mg/mL	C07AB02
	Tablets	100mg	C07AB02
	Tablets	50mg	C07AB02

Active ingredient	Dosage form	Strength	ATC code
Metronidazole	Gel	0.75%	D06BX01
	Injection	500mg	J01XD01
	Suppositories	500mg	P01AB01
	Suspension	200mg/5mL	P01AB01
	Tablets	200mg	P01AB01
Mianserin	Tablets	10mg	N06AX03
	Tablets	30mg	N06AX03
	Cream	2% + 1%	D01AC52, D07XA01
Miconazole Nitrate	Cream	2%	D01AC02
Midazolam	Injection	10mg in 2mL and 5mL Vials	N05CD08
Milrinone	IV Vials	10mg/10mL	C01CE02
Minoxidil	Tablets	10mg	C02DC01
Misoprostol	Tablets	200mcg	A02BB01
Mitomycin	Injection	10mg	L01DC03
Mitoxantrone Hydrochloride	Injection	20mg	L01DB07
Mivacurium Chloride	Injection	10mg/5mL	M03AC10
Moclobemide	Tablets	150mg	N06AG02
Mometasone Furoate	Ointment	0.10%	D07AC13
	Cream	0.10%	D07AC13
Montelukast	Chewable Tablets	4mg	R03DC03
	Chewable Tablets	5mg	R03DC03
	Tablets	10mg	R03DC03
Morphine	Injection	15mg/mL	N02AA01
	Injection	30mg/mL	N02AA01
	Injection	10mg/mL	N02AA01
	Slow-release Tablets	100mg	N02AA01
	Slow-release Tablets	60mg	N02AA01
	Slow-release Tablets	10mg	N02AA01
	Injection	20mg/mL	N02AA01
	Solution	10mg/5mL	N02AA01
	Injection	10mg/mL	N02AA01
	Slow-release Tablets	30mg	N02AA01
Moxifloxacin	Tablets	400mg	J01MA14
Mupirocin	Nasal Ointment	2%	R01AX06
	Ointment	2%	D06AX09
Mycophenolate Mofetil	Syrup		L04AA06
	Infusion	500mg	L04AA06
Mycophenolate Sodium	Gastro-resistant Tablets	180mg	L04AA06
	Gastro-resistant Tablets	360mg	L04AA06
N-Acetylcysteine	Tablets	600mg	V03AB
Naloxone HCl	Injection	400mcg/mL	V03AB15
Naltrexone Hydrochloride	Tablets	50mg	N07BB04
Nandrolone Decanoate	Injection	50mg/mL	A14AB01
Naproxen	Tablets	250mg	M01AE02
Natalizumab	Infusion	20mg/mL	L04AA23

Active ingredient	Dosage form	Strength	ATC code
Natural Surfactant	Vials		R07AA
Neostigmine Methylsulphate	Injection	0.5mg/mL	N07AA01
	Injection	2.5mg/mL	N07AA01
Nevirapine	Oral Suspension	50mg/5mL	J05AG01
	Tablets	200mg	J05AG01
Niclosamide	Tablets	0.5g	P02DA01
Nicorandil	Tablets	10mg	C01DX16
Nicotinamide	Tablets	250mg	A11HA01
Nicotine	Patches	10mg	N07BA01
	Patches	15mg	N07BA01
	Patches	5mg	N07BA01
Nifedipine	Modified-release Tablets	10mg	C08CA05
	Slow release Capsules/ Tablets	20mg	C08CA05
	Capsules		C08CA05
	Tablets/Capsules	10mg	C08CA05
Nimodipine	Injection	200mcg in 50mL	C08CA06
	Tablets	30mg	C08CA06
Nitazoxanide	Syrup	100mg/5mL	P01AX11
	Tablets	500mg	P01AX11
Nitrazepam	Tablets	5mg	N05CD02
Nitrofurantoin	Syrup	25mg/5mL	J01XE01
	Tablets	50mg	J01XE01
Nitrous Oxide	Gas		N01AX13
Nitrous Oxide + Oxygen	Gas	50% + 5%	N01AX63
Noradrenaline	Injection	1:1000 in 2mL	C01CA03
	Injection	2mg/mL	C01CA03
Norethisterone	Tablets	5mg	G03DC02
Norfloxacin	Tablets	400mg	J01MA06
Nortriptyline	Tablets	10mg	N06AA10
	Tablets	25mg	N06AA10
Nystatin	Syrup	100000IU	A07AA02
	Vaginal Cream	100000 IU/4g	G01AA01
Octreotide	Injection	200mcg/mL	H01CB02
	Injection	500mcg/mL	H01CB02
	Injection IM	10mg	H01CB02
	Injection IM	30mg	H01CB02
	Injection IM	20mg	H01CB02
Olanzapine	Vaginal Tablets	5mg	N05AH03
	Tablets	10mg	N05AH03
Omalizumab	Injection	150mg	R03DX05
Omeprazole	Capsules	20mg	A02BC01
	Injection IV	(Paediatric use only)	A02BC01
Ondansetron	Injection	4mg	A04AA01
	Injection	8mg	A04AA01
	Syrup	4mg/5mL	A04AA01
	Tablets	4mg	A04AA01
	Tablets 8mg	8mg	A04AA01
Oral Iron	Tablets/Capsules		B03AA
Oral Rehydration	Powder		A07CA

Active ingredient	Dosage form	Strength	ATC code
Orphenadrine HCl	Tablets	50mg	N04AB02
Oxaliplatin	Vials		L01XA03
Oxybuprocaine	Eye drops	0.4%	S01HA02
Oxybutynin HCl	Syrup	2.5mg/5mL	G04BD04
	Tablets	5mg	G04BD04
Oxytocin	Injection	10 IU/ml	H01BB02
Oxytocin + Ergometrine	Injection	5 IU/ml + 500mcg	G02AC
Paclitaxel	Injection	100mg	L01CD01
	Injection	30mg	L01CD01
Pancreatin	Capsules	10,000U	A09AA02
Pancuronium Bromide	Injection	4mg/2mL	M03AC01
Papaverine	Injection	40mg/mL	G04BE02
Paracetamol	Injection	10mg/mL in 100mL	N02BE01
	Suppositories	100mg or 125mg	N02BE01
	Suppositories	250mg	N02BE01
	Suppositories	500mg	N02BE01
	Syrup	120mg/5mL	N02BE01
	Tablets	500mg	N02BE01
Paroxetine	Tablets	20mg	N06AB05
Pegaspargase	Injection		L01XX24
Pemetrexed	Vials	100mg	L01BA04
	Vials	500mg	L01BA04
Penicillamine	Tablets	250mg	M01CC01
Pentamidine Isethionate	Injection	300mg	P01CX01
	Nebuliser Solution	300mg	P01CX01
Pentazocine Hydrochloride	Tablets	25mg	N02AD01
Pentostatin	Injection	10mg	L01XX02
Pentoxifylline	Tablets	400mg	C04AD03
Perindopril	Tablets	4mg	C09AA04
Permethrin	Cream	5%	P03AC04
	Shampoo	1%	P03AC04
Pethidine Hydrochloride	Injection	50mg/mL	N02AB02
	Injection	100mg/2mL	N02AB02
	Tablets	50mg	N02AB02
Phenobarbitone	Injection	30mg/mL	N03AA02
	Injection	60mg/mL	N03AA02
	Mixture		N03AA02
	Tablets	30mg	N03AA02
Phenol	Injection	5%	C05BB05
Phenol In Water	Injection	6.67%	C05BB05
Hycoline	Solution		D08AE
Phenoxybenzamine HCl	Injection	100mg/2mL	C04AX
Phenoxybenzamine	Capsules	10mg	C04AX02
Phenoxymethylpenicillin	Tablets	250mg	J01CE02
	Solution	125mg/5mL	J01CE02
Phentolamine Mesylate	Injection	10mg/mL	C04AB01
Phenylephrine Hydrochloride	Injection	10mg/mL	C01CA06
	Eye drops	10%	S01FB01, S01GA05
	Eye drops	2.5%	S01FB01, S01GA05

Active ingredient	Dosage form	Strength	ATC code
Phenytoin Sodium	Capsules	50mg	N03AB02
	Capsules	100mg	N03AB02
	Injection	250mg/5mL	N03AB02
	Syrup	30mg/5mL	N03AB02
Phosphate	Enema		A06AG
	Infusion		B05XA
	Tablets Effervescent		A12CX
Phytomenadione (Vitamin K 1)	Injection	10mg	B02BA01
	Injection	10mg/mL in 0.2mL	B02BA01
Pilocarpine Nitrate	Eye drops	2%	S01EB01
Pilocarpine Hydrochloride	Eye drops	1%	S01EB01
	Eye drops	2%	S01EB01
	Eye drops	4%	S01EB01
Pimozide	Tablets	4mg	N05AG02
Piperacillin With Tazobactam	Injection	2.25g	J01CR05
	Injection	4.5g	J01CR05
Pneumococcal	Conjugate Vaccine		J07AL02
	Unconjugated Vaccine		J07AL01
Podophyllotoxin	Cream	0.15%	D06BB04
Polidocanol	Injection	3%	C05BB02
Polio	Vaccine		J07BF03
Polymyxin + Bacitracin	Cream		D06AX
Potash Aluminium (Aluminium Potassium Sulphate)	Sterile Solution for Irrigation	10% w/v	V03AX
Potassium Chloride	IV Infusion		B05XA01
	Tablets	600mg (8mmol)	A12BA01
Potassium Citrate	Mixture	1.5g/5mL	A12BA02
Potassium Phosphate	IV Infusion	2mmol Phosphate, 1.5mmol Potassium and 1.5mmol Sodium per mL	B05XA06
Potassium Chloride	Syrup	1mmol/mL (7.5%)	A12BA01
Potassium Supplement	Tablets Effervescent		A12BA
Potassium Permanganate	Aqueous Solution	1:10000	D08AX06
Povidone-Iodine	Dry Powder Spray	2.50%	D08AG02
	Ointment	10%	D08AG02
	Solution	10%	D08AG02
	Aqueous Solution		D08AG02
	Surgical Scrub	7.50%	D08AG02
	Swab Sticks		D08AG02
	Vaginal Cleanser	10%	G01AX11
Pralidoxime Mesylate	Injection	1g	V03AB04
Praziquantel	Tablets	500mg	P02BA01
Prazosin Hydrochloride	Tablets	1mg	C02CA01
Prednisolone	Retention Enema	20mg in 100mL	A07EA01
	Soluble Tablets	5mg	R03
	Tablets	1mg	H02AB06
	Tablets	5mg	H02AB06
	Tablets Vaginal	5mg	H02AB06
	Eye drops	0.50%	S01BA04

Active ingredient	Dosage form	Strength	ATC code
Pregabalin	Capsules	150mg	N03AX16
	Capsules	300mg	N03AX16
	Capsules	75mg	N03AX16
Prilocaine Hydrochloride + Felypressin	Injection Cartridges	30mg	N01BB54
	Injection	1%	N01BB04
Primaquine	Tablets	7.5mg	P01BA03
Primidone	Tablets	250mg	N03AA03
Procarbazine	Capsules	50mg	L01XB01
Prochlorperazine	Injection	12.5mg/mL	N05AB04
	Tablets	5mg	N05AB04
Procyclidine	Injection IM & IV	10mg/2mL	N04AA04
	Syrup	5mg/5mL	N04AA04
	Tablets	5mg	N04AA04
Progesterone	Injection	50mg/mL	G03DA04
Proguanil Hydrochloride + Atovaquone	Tablets	100mg + 250mg	P01BB51
Promethazine Hydrochloride	Tablets	10mg	R06AD02
	Injection	25mg/mL	R06AD02
	Syrup	5mg/5mL	R06AD02
	Tablets	25mg	R06AD02
Propafenone	Tablets	150mg	C01BC03
Propofol	Injection	10mg/mL in 50mL	N01AX10
	Injection Vials	10mg/mL in 20mL (200mg)	N01AX10
	Pre-filled syringe	10mg/mL in 50mL (500mg)	N01AX10
Propranolol Hydrochloride	Oral Solution	1mg/mL	C07AA05
	Tablets	10mg	C07AA05
	Tablets	40mg	C07AA05
Propylthiouracil	Tablets	50mg	H03BA02
Epoprostenol	Injection	500mcg	B01AC09
Latanoprost	Eye drops		S01EE04
Protamine Sulfate	Injection	50mg/5ml	V03AB14
Protionamide	Tablets	250mg	J04AD01
Omeprazole	Injection IV	40mg	A02BC
Pyrazinamide	Tablets	500mg	J04AK01
Pyridostigmine Bromide	Tablets	60mg	N07AA02
Pyridoxine (Vitamin B 6)	Injection	100mg/mL	A11HA02
	Tablets	10mg	A11HA02
	Tablets	50mg	A11HA02
Pyrimethamine	Tablets	25mg	P01BD01
Pyrimethamine + Sulphadoxine	Tablets	25mg + 500mg	P01BD51
Quetiapine	Tablets	100mg	N05AH04
	Tablets	200mg	N05AH04
	Tablets	25mg	N05AH04

Active ingredient	Dosage form	Strength	ATC code
Quinidine	Tablets	Tablets 200mg or Modified Release Tablets 250mg	C01BA01
	Tablets	300mg	P01BC01
	Injection	300mg	P01BC01
Rabies	Vaccine		J07BG01
Ranitidine	Injection	50mg	A02BA02
	Syrup		A02BA02
	Tablets	150mg	A02BA02
Rasagiline	Tablets	1mg	N04BD02
Rasburicase	Injection	1.5mg	V03AF07
	Injection	7.5mg	V03AF07
Recombinant Human Erythropoietin	Pre-filled syringe	2000 IU	B03XA01
	Pre-filled syringe	4000 IU	B03XA01
	Pre-filled syringe	3000 IU	B03XA01
Remifentanil Hydrochloride	Injection	1mg	N01AH06
Rifabutin	Capsules	150mg	J04AB04
Rifampicin	Capsules	300mg	J04AB02
	Injection	600mg/10mL	J04AB02
	Syrup	100mg/5mL	J04AB02
Rifampicin + Isoniazid	Tablets	150mg + 100mg	J04AM02
	Tablets	300mg + 150mg	J04AM02
Ringer'S Solution For Injection (Compound Sodium Chloride)	IV Infusion	Sodium 147mmol/L, Potassium 4mmol/L, Calcium 2mmol/L, Chloride 156mmol/L per 1000mL	B05CX10
Risperidone	Depot Injection	25mg	N05AX08
	Depot Injection	37.5mg	N05AX08
	Depot Injection	50mg	N05AX08
	Syrup	1mg/mL in 100mL	N05AX08
	Tablets	1mg	N05AX08
	Tablets	2mg	N05AX08
Ritonavir	Capsules	100mg	J05AE03
Rituximab	Injection	100mg	L01XC02
	Injection	500mg	L01XC02
Rivaroxaban	Tablets	10mg	B01AX06
Rocuronium Bromide	Injection	10mg/mL	M03AC09
Ropinirole	Tablets	1mg	N04BC04
	Tablets	250mcg	N04BC04
	Tablets	5mg	N04BC04
Rosuvastatin	Tablets	20mg	C10AA07
	Tablets	40mg	C10AA07
Rufinamide	Tablets	200mg	N03AF03
Salbutamol	Inhaler	100mcg/pugg	R03AC02
	Injection	5mg/5mL	R03CC02
	Respiratory Solution	5mg/mL	R03AC02
	Syrup	2mg/5mL	R03CC02
	Tablets	4mg	R03CC02

Active ingredient	Dosage form	Strength	ATC code
Salicylic Acid + Betamethasone	Ointment	3% + 0.05%	D07XC01
Salicylic Acid + Clobetasol	Cream		EXTEMP
Salicylic Acid In Betamethasone Lotion	Scalp application	2% + 0.05%	D07XC01
Salmeterol	Inhaler		R03AC12
Saquinavir	Capsules	500mg	J05AE01
Selegiline	Tablets	5mg	N04BD01
Senna	Tablets	7.5mg	A06AB06
Sevoflurane	Inhalation anaesthetic		N01AB08
Silicone	Injection	100% V/V in 10mL	S01XA
Silver Sulphadiazine	Cream	1%	D06BA01
Simvastatin	Tablets	10mg	C10AA01
	Tablets	20mg	C10AA01
	Tablets	40mg	C10AA01
	Tablets	80mg	C10AA01
Sirolimus	Tablets	1mg	L04AA10
Sodium Aurothiomalate	Injection	10mg	M01CB01
Sodium Bicarbonate	Pre-filled syringe	8.4% in 10mL	B05XA02
	Pre-filled syringe	8.4% in 50mL	B05XA02
	Pre-filled syringe	8.4% in 200mL	B05XA02
	Tablets	500/600mg	A12CA
Sodium Calcium Edetate	Injection	1g	V03AB03
Sodium Chloride	Injection IV	30%	B05XA03
	Injection (Irrigation)	0.9% in 3L	B05CB01
	Injection (Irrigation)	0.9% in 500mL	B05XA03
	Injection IV	0.225% in 500mL	B05XA03
	Injection IV	0.45% in 500mL	B05XA03
	Injection IV	0.9% in1000mL	B05XA03
	Injection IV	0.9% in 100mL	B05XA03
	Injection IV	0.9% in 10mL	B05XA03
	Injection IV	0.9% in 20mL	B05XA03
	Injection IV	0.9% in 250mL	B05XA03
	Injection IV	0.9% in 2mL Ampoules	B05XA03
	Injection IV	0.9% in 3000mL	B05XA03
	Injection IV	0.9% in 500mL	B05XA03
	Injection IV	0.9% in 50mL	B05XA03
Sodium Citrate	Bladder Irrigation	3.8% in 20mL	B05CB02
	Solution	0.3M	B05CB02
Sodium Cromoglicate	Eye drops	2%	S01GX01
Sodium Dichloroisocyanurate (Disinfectant Granules)	Granules		D08AX

Active ingredient	Dosage form	Strength	ATC code
Sodium Feredetate (Oral Iron)	Solution	190mg in 5mL equivalent to 27.5mg iron	B03AB03
Sodium Hyaluronate	Injection	10mg/mL	M09AX01
Sodium Lactate Compound	Injection IV	In 1000mL	B05CX10
	Injection IV	In 500mL	B05CX10
Sodium Nitrite	Injection	300mg (3%W/V)	V03AB08
Sodium Nitroprusside	Injection	50mg	C02DD01
Sodium Stibogluconate	Injection	10G	P01CB02
Sodium Tetradecyl Sulphate	Injection	1% in 2mL	C05BB04
	Injection	3% in 2mL	C05BB04
Sodium Thiosulphate	Injection	25% w/v	V03AB06
Sodium Valproate	Controlled-release Tablets	200mg	N03AG01
	Controlled-release Tablets	500mg	N03AG01
	Injection	400mg	N03AG01
	Syrup	40mg/ml in 5mL	N03AG01
Sodium Aurothiomalate	Injection	50mg/0.5mL	M01CB01
Sotalol	Tablets	80mg	C07AA07
Spectinomycin	Injection	2g	J01XX04
Spironolactone	Tablets	100mg	C03DA01
	Tablets	25mg	C03DA01
Streptomycin Sulphate	Injection	1g	J01GA01
Sucralfate	Oral Liquid	1g/5mL	A02BX02
Sufentanil	Injection	0.0075mg/mL	N01AH03
	Injection	50mcg/mL	N01AH03
Sulfadiazine	Tablets	500mg	J01EC02
Sulfasalazine	Oral Liquid	250mg/5mL	A07EC01
	Suppositories	500mg	A07EC01
	Tablets	500mg	A07EC01
Sulpiride	Capsules	50mg	N05AL01
	Suspension	40mg/mL	N05AL01
	Tablets	200mg	N05AL01
Sunitinib	Capsules	12.5mg	L01XE04
	Capsules	50mg	L01XE04
Suxamethonium Chloride	Injection	100mg/2mL	M03AB01
Tacrolimus	Capsules	0.5mg	L04AA05
	Capsules	1mg	L04AA05
	Capsules	5mg	L04AA05
Tamoxifen	Tablets	20mg	L02BA01
Tannic Acid	Powder		A07XA
Teicoplanin	Injection	200mg	J01XA02
Temazepam	Oral Solution	10mg/5mL	N05CD07
Temozolomide	Capsules	100mg	L01AX03
	Capsules	140mg	L01AX03
	Capsules	20mg	L01AX03
	Capsules	5mg	L01AX03
Tenofovir	Tablets	245mg	J05AF07
Terbutaline	Dry Powder Inhaler	500mcg	R03AC03

Active ingredient	Dosage form	Strength	ATC code
Teriflunomide	Tablets	14mg	L04AA31
Teriparatide	Pre-filled pen	20mcg/80mcL	H05AA02
Terlipressin Acetate	Injection IV	1mg	H01BA04
Testosterone Enantate Depot	Injection	250mg	G03BA03
Testosterone Undecanoate	Injection	1000mg/4mL	G03BA03
Tetanus	Immunoglobulin	250 IU	J06BB02
Tetanus Or Diphtheria (Adsorbed) + Tetanus	Vaccine	ADULT	J07AM51
Tetrabenazine	Tablets	25mg	N05AK01
Tetracosactide (Tetracosactrin)	Injection	0.25mg	H01AA02
Tetracycline	Capsules	250mg	J01AA07
Thalidomide	Capsules/ Tablets	50mg	L04AX02
Theophylline	Tablets	250mg	R03DA04
Thiamine (Vitamin B1)	Tablets	50mg	A11DA01
Thiopental Sodium (Thiopentone Sodium)	Injection	0.5g	N01AF03, N05CA19
Tigecycline	Vials	50mg	J01AA12
Timolol Maleate	Eye drops	0.25%	S01ED01
	Eye drops	0.50%	S01ED01
Tioguanine	Tablets	40mg	L01BB03
Tobramycin	Eye drops	0.30%	S01AA12
	Injection	40mg/mL	J01GB01
Topiramate	Tablets	100mg	N03AX11
	Tablets	200mg	N03AX11
	Tablets	25mg	N03AX11
	Tablets	50mg	N03AX11
Trabectedin	Vials	0.25mg	L01CX01
	Vials	1mg	L01CX01
Tramadol	Capsules	50mg	N02AX02
	Injection	100mg	N02AX02
Tranexamic Acid	Injection	500mg/5mL	B02AA02
	Tablets	500mg	B02AA02
Trastuzumab	Vials	150mg	L01XC03
Travoprost	Eye drops		S01EE04
Tretinoin	Capsules	10mg	L01XX14
Triamcinolone	Injection	40mg/mL	H02AB08
Triclosan	Skin cleanser	2%	D08AE04
Trifluoperazine	Tablets	5mg	N05AB06
Benzhexol Hydrochloride	Tablets	2mg	N04AA01
Trimetazidine Hydrochloride	Tablets	20mg	C01EB15
Trimethoprim	Tablets	100mg	J01EA01
Tropicamide	Eye drops	0.5%	S01FA06
	Eye drops	1%	S01FA06
Tuberculin Mantoux	Vaccine		V04CF01
Typhoid	Vaccine		J07AP
Urokinase	Injection	10,000 IU	B01AD04
	Injection	50,000 IU	B01AD04
Ursodeoxycholic Acid	Tablets	150mg	A05AA02
	Capsules	250mg	A05AA02

Active ingredient	Dosage form	Strength	ATC code
Valganciclovir	Tablets	450mg	J05AB14
Vancomycin	Capsules	125mg	A07AA09
	Injection	500mg	J01XA01
Varicella Zoster	Vaccine	2000 PFU	J07BK01
	Immunoglobulin		J06BB03
Vecuronium Bromide	Injection	10mg	M03AC03
Venlafaxine Hydrochloride	Modified release Capsules	75mg	N06AX16
Verapamil	Injection	5mg/2mL	C08DA01
	Slow release Tablets	240mg	C08DA01
	Tablets	40mg	C08DA01
Vigabatrin	Sachets	500mg	N03AG04
	Tablets	500mg	N03AG04
Vinblastine Sulphate	Injection	10mg/10mL	L01CA01
Vincristine Sulphate	Injection	2mg/2mL	L01CA02
Vinorelbine	Injection	10mg/mL in 5mL	L01CA04
Warfarin	Tablets	1mg	B01AA03
	Tablets	3mg	B01AA03
	Tablets	5mg	B01AA03
Xylomethazoline HCl	Nasal drops	0.10%	R01AA07
	Nasal drops	0.05%	R01AA07
Yellow Fever	Vaccine		J07BL01
Zidovudine + Lamivudine	Tablets	300mg + 150mg	J05AF30
Zidovudine	Capsules	100mg	J05AF01
	Injection	10mg/mL	J05AF01
	Oral Solution	100mg/10mL	J05AF01
Zoledronic Acid	Vials	5mg	M05BA08
	Vials	4mg	M05BA08
Zuclopenthixol	Injection	50mg	N05AF05
	Injection	200mg	N05AF05
	Tablets	10mg	N05AF05
	Tablets	25mg	N05AF05
	Tablets	2mg	N05AF05

APPENDIX 6

Centrally authorised products not sourced by the Malta National Health Service

ATC Code	Product not sourced by the Malta National Health Service
A02BC02	Pantoprazole
A02BC05	Esomeprazole
A04AA02	Granisetron
A04AA05	Palonosetron
A04AD12	Fosaprepitant
A05AA03	Cholic Acid
A06AH01	Methylnaltrexone Bromide
A06AH03	Naloxegol
A06AX04	Linaclotide
A06AX05	Prucalopride
A07AA12	Fidaxomicin
A08AB01	Orlistat
A10	Dulaglutide
A10BD05	Pioglitazone / Metformin
A10BD06	Pioglitazone / Glimepiride
A10BD07	Sitagliptin / Metformin
A10BD08	Vildagliptin / Metformin
A10BD09	Alogliptin / Pioglitazone
A10BD10	Saxagliptin / Metformin Hydrochloride
A10BD11	Linagliptin / Metformin Hydrochloride
A10BD13	Alogliptin / Metformin
A10BD15	Dapagliflozin / Metformin
A10BD16	Canagliflozin / Metformin
A10BD20	Empagliflozin / Metformin
A10BG03	Pioglitazone
A10BH01	Sitagliptin / Metformin Hydrochloride
A10BH02	Vildagliptin
A10BH03	Saxagliptin
A10BH04	Alogliptin Benzoate
A10BH05	Linagliptin
A10BX02	Repaglinide
A10BX03	Nateglinide
A10BX04	Exenatide
A10BX07	Liraglutide
A10BX09	Dapagliflozin
A10BX10	Lixisenatide
A10BX11	Canagliflozin
A10BX12	Empagliflozin
A10BX13	Albiglutide
A11HA08	Tocofersolan
A16AA04	Mercaptamine Bitartrate
A16AA05	Carglumic Acid
A16AA06	Betaine Anhydrous

ATC Code	Product not sourced by the Malta National Health Service
A16AB	Galsulfase
A16AB02	Imiglucerase
A16AB03	Agalsidase Alfa
A16AB04	Agalsidase Beta
A16AB05	Laronidase
A16AB07	Alglucosidase Alfa
A16AB09	Idursulfase
A16AB10	Velaglucerase Alfa
A16AB12	Elosulfase Alfa
A16AX04	Nitisinone
A16AX06	Miglustat
A16AX07	Sapropterin
A16AX08	Teduglutide
A16AX10	Eliglustat
B01	Vorapaxar
B01AB02	Antithrombin Alfa
B01AC16	Eptifibatide
B01AC22	Prasugrel
B01AC24	Ticagrelor
B01AD08	Reteplase
B01AE06	Bivalirudin
B01AE07	Dabigatran Etexilate
B01AF02	Apixaban
B01AX01	Defibrotide
B01AX05	Fondaparinux Sodium
B02BD02	Turoctocog Alfa
B02BD04	Nonacog Gamma
B02BD09	Nonacog Alfa
B02BD11	Catridecacog
B02BX05	Eltrombopag
B03	Ferumoxytol
B03XA01	Epoetin Beta
B03XA02	Darbepoetin Alfa
B03XA03	Methoxy Polyethylene Glycol-Epoetin Beta
B06AC01	C1 Inhibitor (Human)
B06AC04	Conestat Alfa
C01BD07	Dronedarone
C01BG11	Vernakalant Hydrochloride
C01EB17	Ivabradine
C01EB18	Ranolazine
C01EB19	Icatibant
C01EB21	Regadenoson
C02KX02	Ambrisentan

ATC Code	Product not sourced by the Malta National Health Service
C02KX04	Macitentan
C02KX05	Riociguat
C03XA01	Tolvaptan
C09CA04	Irbesartan
C09CA07	Telmisartan
C09CA09	Azilsartan Medoxomil
C09DA04	Irbesartan / Hydrochlorothiazide
C09DA07	Telmisartan / Hydrochlorothiazide
C09DB01	Amlodipine/ Valsartan
C09DB04	Telmisartan / Amlodipine
C09XA02	Aliskiren
C09XA52	Aliskiren / Hydrochlorothiazide
C09XA53	Aliskiren / Amlodipine
C10 AX10	Alipogene Tiparvovec
C10AC04	Colesevelam
C10AX12	Lomitapide
D02BB02	Afamelanotide
D03BA03	Concentrate Of Proteolytic Enzymes Enriched In Bromelain
D06AX13	Retapamulin
D06BB10	Imiquimod
D06BX02	Ingenol Mebutate
D11AX	Eflornithine
G03AA13	Norelgestromin / Ethinyl Estradiol
G03AA14	Nomegestrol / Estradiol
G03AD02	Ulipristal Acetate
G03GA07	Lutropin Alfa
G03GA08	Choriogonadotropin Alfa
G03GA09	Corifollitropin Alfa
G03XB02	Ulipristal
G03XC01	Raloxifene
G03XC02	Bazedoxifene
G03XC05	Ospemifene
G04BD10	Darifenacin Hydrobromide
G04BD11	Fesoterodine
G04BD12	Mirabegron
G04BE08	Tadalafil
G04BE09	Vardenafil
G04BE10	Avanafil
G04CA04	Silodosin
H01AB01	Thyrotropin Alfa
H01AC01	Somatropin
H01AC03	Mecasermin
H01CB05	Pasireotide

ATC Code	Product not sourced by the Malta National Health Service
H01CC01	Ganirelix
H01CC02	Cetrorelix
J01	Tedizolid Phosphate
J01DI02	Ceftaroline Fosamil
J01FA15	Telithromycin
J01XA03	Telavancin
J01XA04	Dalbavancin
J01XA05	Oritavancin
J02AX05	Micafungin
J02AX06	Anidulafungin
J04A	Bedaquiline
J04AA01	Para-Aminosalicylic Acid
J04AK06	Delamanid
J05	Darunavir / Cobicistat
J05AB04	Ribavirin
J05AE	Boceprevir
J05AE01	Saquinavir
J05AE02	Indinavir
J05AE03	Ritonavir
J05AE07	Fosamprenavir
J05AE08	Atazanavir Sulphate
J05AE09	Tipranavir
J05AE10	Darunavir
J05AE14	Simeprevir
J05AF04	Stavudine
J05AF08	Adefovir Dipivoxil
J05AF09	Emtricitabine
J05AF10	Entecavir
J05AF11	Telbivudine
J05AG04	Etravirine
J05AG05	Rilpivirine
J05AR03	Emtricitabine / Tenofovir Disoproxil
J05AR08	Emtricitabine / Rilpivirine / Tenofovir Disoproxil
J05AR09	Elvitegravir / Cobicistat / Emtricitabine / Tenofovir Disoproxil
J05AX07	Enfuvirtide
J05AX11	Elvitegravir
J05AX12	Dolutegravir
J05AX14	Daclatasvir
J05AX15	Sofosbuvir
J07BA02	Japanese-Encephalitis Vaccine (Inactivated, Adsorbed)
J07BB01	Pandemic Influenza Vaccine (H5N1) (Whole Virion, Inactivated, Adsorbed)
J07BB02	Pandemic Influenza Vaccine (H5N1) (Split Virion, Inactivated, Adjuvanted)
J07BBOI	Prepandemic Influenza Vaccine (H5N1) (Whole Virion, Inactivated,Prepared In Cell Culture)
J07BC01	Hepatitis-B Vaccine (RDNA)

ATC Code	Product not sourced by the Malta National Health Service
J07BC20	HepatitisA (Inactivated) And Hepatitis B (Rdna) (Hab) Vaccine (Adsorbed)
J07BD04	Measles, Mumps, Rubella And Varicella Vaccine (Live)
J07BD52	Measles, Mumps And Rubella Vaccine (Live)
J07BH01	Rotavirus Vaccine, Live, Attenuated
J07BH02	Rotavirus Vaccine, Live, Oral
J07BK02	Zoster Vaccine (Live)
J07BX	Modified Vaccinia Ankara Virus
J07CA09	Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (Rdna), Poliomyelitis (Inactivated) And Haemophilus Influenzae Type-B Conjugate Vaccine (Adsorbed)
L01	Olaparib
L01AB01	Busulfan
L01AC01	Thiotepa
L01BB06	Clofarabine
L01BB07	Nelarabine
L01BC06	Capecitabine
L01BC08	Decitabine
L01BC53	Tegafur / Gimeracil / Oteracil
L01CA05	Vinflunine
L01CD	Cabazitaxel
L01CX01	Trabectedin
L01DB11	Pixantrone Dimaleate
L01XC	Ramucirumab
L01XC06	Cetuximab
L01XC08	Panitumumab
L01XC09	Catumaxomab
L01XC10	Ofatumumab
L01XC11	Ipilimumab
L01XC12	Brentuximab Vedotin
L01XC13	Pertuzumab
L01XC15	Obinutuzumab
L01XD04	5-Aminolevulinic Acid Hydrochloride
L01XD05	Temoporfin
L01XE	Ceritinib
L01XE02	Gefitinib
L01XE05	Sorafenib
L01XE07	Lapatinib
L01XE09	Temsirolimus
L01XE11	Pazopanib
L01XE13	Afatinib
L01XE14	Bosutinib
L01XE15	Vemurafenib
L01XE16	Crizotinib
L01XE17	Axitinib

ATC Code	Product not sourced by the Malta National Health Service
L01XE18	Ruxolitinib
L01XE21	Regorafenib
L01XE23	Dabrafenib
L01XE24	Ponatinib
L01XE25	Trametinib
L01XE27	Ibrutinib
L01XX05	Hydroxycarbamide
L01XX17	Topotecan
L01XX22	Alitretinoin
L01XX23	Mitotane
L01XX27	Arsenic Trioxide
L01XX41	Eribulin
L01XX43	Vismodegib
L01XX44	Aflibercept
L01XX47	Idelalisib
L02BA02	Toremifene
L02BA03	Fulvestrant
L02BX02	Degarelix
L02BX03	Abiraterone
L03AA02	Filgrastim
L03AA13	Pegfilgrastim
L03AA14	Lipegfilgrastim
L03AB10	Peginterferon Alfa-2B
L03AB11	Peginterferon Alfa-2A
L03AB13	Peginterferon Beta-1A
L03AX11	Tasonermin
L03AX14	Histamine Dihydrochloride
L03AX15	Mifamurtide
L03AX16	Plerixafor
L04AA	Vedolizumab
L04AA14	Anakinra
L04AA24	Abatacept
L04AA25	Eculizumab
L04AA26	Belimumab
L04AA28	Belatacept
L04AA31	Teriflunomide
L04AA32	Apremilast
L04AB05	Certolizumab Pegol
L04AB06	Golimumab
L04AC05	Ustekinumab
L04AC07	Tocilizumab
L04AC08	Rilonacept
L04AC10	Secukinumab

ATC Code	Product not sourced by the Malta National Health Service
L04AC11	Siltuximab
L04AX05	Pirfenidone
M01AH04	Parecoxib
M03AX01	Botulinum Toxin Type B
M04AA03	Febuxostat
M04AX02	Pegloticase
M05BA06	Ibandronic Acid
M05BB03	Alendronic Acid / Colecalciferol
M05BC01	Dibotermin Alfa
M05BC02	Eptotermin Alfa
M05BX03	Strontium Ranelate
M05BX04	Denosumab
M09AB02	Collagenase Clostridium Histolyticum
M09AX02	Matrix-Applied Characterised Autologous Cultured Chondrocytes
N01BB20	Lidocaine / Prilocaine
N01BX04	Capsaicin
N02BG08	Ziconotide
N03AF04	Eslicarbazepine Acetate
N03AX17	Stiripentol
N03AX18	Lacosamide
N03AX21	Retigabine
N03AX22	Perampanel
N04B	Safinamide
N04BC05	Pramipexole
N04BC09	Rotigotine
N04BX01	Tolcapone
N04BX02	Entacapone
N05AE05	Lurasidone
N05AH01	Loxapine
N05AH05	Asenapine
N05AX12	Aripiprazole
N05AX13	Paliperidone
N05CF03	Zaleplon
N05CH01	Melatonin
N05CM18	Dexmedetomidine
N06AX21	Duloxetine
N06AX22	Agomelatine
N06AX26	Vortioxetine
N06BC01	Caffeine
N06DA03	Rivastigmine
N06DX01	Memantine Hydrochloride
N07BA03	Varenicline
N07BB05	Nalmefene

ATC Code	Product not sourced by the Malta National Health Service
N07BC51	Buprenorphine / Naloxone
N07XX05	Amifampridine
N07XX07	Fampridine
N07XX08	Tafamidis
N07XX59	Dextromethorphan Hydrobromide / Quinidine Sulfate
P01BF05	Piperaquine Tetraphosphate / Dihydroartemisinin
R03AC18	Indacaterol
R03AL	Aclidinium Bromide / Formoterol
R03AL03	Umeclidinium Bromide / Vilanterol
R03AL04	Indacaterol / Glycopyrronium Bromide
R03AL05	Aclidinium / Formoterol Fumarate Dihydrate
R03BB	Aclidinium Bromide
R03BB06	Glycopyrronium Bromide
R03BB07	Umeclidinium Bromide
R03DX07	Roflumilast
R06AX27	Desloratadine / Pseudoephedrine
R07AX	Nitric Oxide
R07AX02	Ivacaftor
S01	Brinzolamide / Brimonidine Tartrate
S01BC10	Nepafenac
S01BC11	Bromfenac
S01EC04	Brinzolamide
S01ED51	Brinzolamide / Timolol
S01EE03	Bimatoprost
S01EE04	Travoprost
S01GX06	Emedastine
S01GX09	Olopatadine
S01LA01	Verteporfin
S01LA03	Pegaptanib
S01LA04	Ranibizumab
S01XA18	Ciclosporin
S01XA19	Ex Vivo Expanded Autologous Human Corneal Epithelial Cells Containing Stem Cells
S01XA22	Ocriplasmin
V	Copper (64Cu) Chloride
V03AB17	Methylthioninium Chloride
V03AC02	Deferiprone
V03AE02	Sevelamer Carbonate
V03AE05	Mixture Of Polynuclear Iron(Iii)-Oxyhydroxide, Sucrose And Starches
V03AF02	Dexrazoxane
V03AF08	Palifermin
V03AX03	Cobicistat
V04CX	13C-Urea
V04D	Sulesomab

ATC Code	Product not sourced by the Malta National Health Service
V08CA06	Gadoversetamide
V08DA01	Perflutren
V08DA04	Sulphur Hexafluoride
V09	Yttrium [90Y] Chloride
V09AB03	Ioflupane (123L)
V09AX04	Flutemetamol (18F)
V09AX05	Florbetapir (18F)
V09AX06	Florbetaben(18F)
V09HA03	Besilesomab
V09IA09	Tilmanocept
V10BX02	Samarium [153Sm] Lexidronam Pentasodium
V10XX02	Ibritumomab Tiuxetan
V10XX03	Radium Ra223 Dichloride

APPENDIX 7

Centrally authorised products not sourced by the Malta National Health Service by indication

Medicine Name	Indication
Abilify	Abilify is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
Abilify Maintena	Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.
Abseamed	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients.
Accofil	Accofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy
Actelsar HCT	Treatment of essential hypertension.
Actos	Pioglitazone is indicated in the treatment of type-2 diabetes mellitus: as monotherapy: in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate
Adasuve	Adasuve is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms.
Adcetris	Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL)
Adcirca (previously Tadalafil Lilly)	Adcirca is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as World Health Organization functional class II and III, to improve exercise capacity.
Adempas	Chronic thromboembolic pulmonary hypertension (CTEPH)
Adenuric	Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
Adjupanrix (previously Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals)	Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.
Adrovance	Treatment of postmenopausal osteoporosis in patients at risk of vitamin-D insufficiency.
Advate	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency)..
Aerius	Aerius is indicated for the relief of symptoms associated with: allergic rhinitis; urticaria.
Aflunov	Active immunisation against H5N1 subtype of influenza-A virus.
Aldara	Imiquimod cream is indicated for the topical treatment of external genital and perianal warts (condylomata acuminata) in adults; small superficial basal-cell carcinomas (sBCCs) in adults; clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratosis.
Aldurazyme	Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis I (MPS I; alpha-L-iduronidase deficiency) to treat the nonneurological manifestations of the disease.
Alli (previously Orlistat GSK)	Alli is indicated for weight loss in adults who are overweight (body mass index, BMI, 28 kg/m2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

Medicine Name	Indication
Aloxi	Aloxi is indicated in adults for: the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.
Altargo	Short term treatment of the following superficial skin infections: impetigo, infected small lacerations, abrasions, or sutured wounds.
Ambirix	Ambirix is for use in non-immune persons from one year up to and including 15 years of agefor protection against hepatitis-A and hepatitis-B infection.
Ameluz	Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2).
Amyvid	Amyvid is a radiopharmaceutical indicated for positron-emission-tomography (PET) imaging of amyloid neuritic plaque density in the brains of adult patients with cognitive impairment.
Angiox	Angiox is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary PCI.
Anoro	Anoro is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Aprovel	Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type-2 diabetes mellitus as part of an antihypertensive medicinal-product regimen.
Aptivus	Aptivus, co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pretreated adults and adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.
Aranesp	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients. Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.
Ariclaim	Treatment of diabetic peripheral neuropathic pain.Ariclaim is indicated in adults.
Arixtra	Prevention of venous thromboembolic events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip-replacement surgery.
Arzerra	Treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab.
Atriance	Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.
ATryn	ATryn is indicated for the prophylaxis of venous thromboembolism in surgery of patients with congenital antithrombin deficiency. ATryn is normally given in association with heparin or low molecular weight heparin.
Aubagio	Treatment of adult patients with relapsing-remitting multiple sclerosis (MS).
Axura	Treatment of patients with moderate to severe Alzheimer's disease.

Medicine Name	Indication
Azarga	Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.
Azomyr	Azomyr is indicated for the relief of symptoms associated with allergic rhinitis; urticaria.
Azopt	Azopt is indicated to decrease elevated intraocular pressure in: ocular hypertension; open-angle glaucomaas monotherapy in adultpatients unresponsive to beta-blockers or in adultpatients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers or prostaglandin analogues.
Baraclude	Baraclude is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with: compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels.
BeneFIX	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor-IX deficiency).
Benlysta	Benlysta is indicated as add-on therapy in adult patients with active, auto-antibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.
Beromun	Beromun is indicated in adults as an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft-tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).
Betmiga	Symptomatic treatment of urgency.Increased micturition frequency and / or urgency incontinence as may occur in adult patients with overactive-bladdersyndrome.
Binocrit	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients: treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis; in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.
Biograstim	Biograstim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.
Biopoin	Treatment of symptomatic anaemia associated with chronic renal failure in adult patients. Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.
Bondronat	Bondronat is indicated for: prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases; treatment of tumour-induced hypercalcaemia with or without metastes.
Bonviva	Treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Medicine Name	Indication
Bosulif	Bosulif is indicated for the treatment of adult patients with chronic-phase, accelerated-phaseand blast-phasePhiladelphia-chromosome-positive chronic myelogenous leukaemiapreviously treated with one or more tyrosine-kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
Bretaris Genuair	Bretaris Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Brilique	Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with - acute coronary syndromes (ACS) or - a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.
Brimica Genuair	Brimica Genuair is indicated as a maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Brinavess	Rapid conversion of recent-onset atrial fibrillation to sinus rhythm in adults: for non-surgery patients: atrial fibrillation 7 days duration; for post-cardiac-surgery patients: atrial fibrillation 3 days duration.
Brintellix	Treatment of major depressive episodes in adults
Busilvex	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.
Busulfan Fresenius Kabi	Busulfan Fresenius Kabi followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.
Bydureon	Bydureon is indicated for treatment of type-2 diabetes mellitus in combination with: metformin; sulphonylurea; thiazolidinedione; metformin and sulphonylurea; metformin and thiazolidinedione; in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.
Byetta	Byetta is indicated for treatment of type-2 diabetes mellitus in combination with: metformin; sulphonylureas; thiazolidinediones; metformin and a sulphonylurea; metformin and a thiazolidinedione; in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Byetta is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these medicinal products.
Capecitabine Accord	Capecitabine Accord is indicated for the treatment of: -for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. - metastatic colorectal cancer. - first-line treatment of advanced gastric cancer in combination with a platinumbased regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracyclinecontaining chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Medicine Name	Indication
Capecitabine Medac	Capecitabine Medac is indicated for the treatment of: -for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. - metastatic colorectal cancer. - first-line treatment of advanced gastric cancer in combination with a platinumbased regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracyclinecontaining chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Capecitabine SUN	Capecitabine is indicated for the treatment of: -for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. - metastatic colorectal cancer. - first-line treatment of advanced gastric cancer in combination with a platinumbased regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracyclinecontaining chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Capecitabine Teva	Capecitabine Teva is indicated for the treatment of: -for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. - metastatic colorectal cancer. - first-line treatment of advanced gastric cancer in combination with a platinumbased regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracyclinecontaining chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Caprelsa	Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.
Carbaglu	Carbaglu is indicated in treatment of: hyperammonaemia due to N-acetylglutamate-synthase primary deficiency; hyperammonaemia due to isovaleric acidaemia; hyperammonaemia due to methymalonic acidaemia; hyperammonaemia due to propionic acidaemia.
Celvapan	Prophylaxis of influenza caused by A(H1N1)v 2009 virus. Celvapan should be used in accordance with official guidance.
Ceplene	Ceplene maintainance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.

Medicine Name	Indication
Cerdelga	Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).
Cerezyme	Cerezyme (imiglucerase) is indicated for use as longterm enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.
Cetrotide	Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte-pick-up and assisted-reproductive techniques.
Champix	Champix is indicated for smoking cessation in adults.
Cholestagel	Cholestagel co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMG-CoA)-reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density-lipoprotein-cholesterol (LDL-C) levels in adult patients
ChondroCelect	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults.
Cialis	Treatment of erectile dysfunction.
Cimzia	Cimzia, in combination with methotrexate (MTX), is indicated for: • the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate. • the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. • the treatment of adult patients with severe active axial spondyloarthritis, comprising: • adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). • the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.
Cinryze	Treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE).
Circadin	Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
CoAprovel	Treatment of essential hypertension. This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.
Colobreathe	Colobreathe is indicated for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) agedsix years and older.
Cometriq	Treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.
Competact	Competact is indicated in the treatment of type-2-diabetes-mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
Comtan	Entacapone is indicated as an adjunct to standard preparations of levodopa / benserazide or levodopa / carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.

Medicine Name	Indication
Comtess	Entacapone is indicated as an adjunct to standard preparations of levodopa / benserazide or levodopa / carbidopa for use in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.
Conbriza	Conbriza is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture.
Constella	Constella is indicated for the symptomatic treatment of moderate to severe irritable-bowel syndrome with constipation (IBS-C) in adults.
Controloc Control	Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
Copalia	Treatment of essential hypertension. Copalia is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.
Corlentor	Symptomatic treatment of chronic stable angina pectoris Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated: - in adults unable to tolerate or with a contra-indication to the use of beta-blockers - or in combination with beta-blockers in patients inadequately controlled with an optimal beta- blocker dose. Treatment of chronic heart failure Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.
Cosentyx	Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Crixivan	Crixivan is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected adults.
Cuprymina	Cuprymina is a radiopharmaceutical precursor. This medicinal product must be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.
Cymbalta	Treatment of major depressive disorder. Treatment of diabetic peripheral neuropathic pain. Treatment of generalised anxiety disorder.
Cyramza	Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
Cystadane	Adjunctive treatment of homocystinuria, involving deficiencies or defects in: cystathionine beta-synthase (CBS); 5,10-methylene-tetrahydrofolate reductase (MTHFR); cobalamin cofactor metabolism (cbl).
Cystagon	Cystagon is indicated for the treatment of proven nephropathic cystinosis.
Dacogen	Treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organization (WHO) classification, who are not candidates for standard induction chemotherapy.

Medicine Name	Indication
Dafiro	Treatment of essential hypertension. Dafiro is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.
Daklinza	Daklinza is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.
Daliresp	Daliresp is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted).
Dasselta	Dasselta is indicated for the relief of symptoms associated with allergic rhinitis; urticaria.
DaTSCAN	DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:In adult patients with clinically uncertain Parkinsonian syndromes.
Daxas	Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis.
Defitelio	Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.
Deltyba	Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.
Desloratadine Actavis	Treatment of allergic rhinitis and urticaria.
Desloratadine ratiopharm	Relief of symptoms associated with allergic rhinitis; urticaria.
Desloratadine Teva	Desloratadine Teva is indicated for the relief of symptoms associated with allergic rhinitis; urticaria.
Dexdor	For sedation of adultintensive 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).
Diacomit	Diacomit is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome).
Dificlir	Dificlir is indicated in adults for the treatment of Clostridium difficile infections (CDI) also known as C. difficile-associated diarrhoea (CDAD). Consideration should be given to official guidelines on the appropriate use of antibacterial agents.
Duaklir Genuair	Duaklir Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Duloxetine Lilly	Duloxetine Lilly is indicated in adults for:Treatment of major depressive disorderTreatment of diabetic peripheral neuropathic painTreatment of generalised anxiety disorderDuloxetine Lilly is indicated in adults.
DuoTrav	Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
Dynastat	For the short-term treatment of postoperative pain in adults.
Ebixa	Treatment of patients with moderate to severe Alzheimer's disease.
Ecalta	Treatment of invasive candidiasis in adult non-neutropenic patients.

Medicine Name	Indication
Ecansya (previously Capecitabine Krka)	Ecansya is indicated for the adjuvant treatment of patients following surgery of stage-III (Dukes stage-C) colon cancer. Ecansya is indicated for the treatment of metastatic colorectal cancer. Ecansya is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated
Edarbi	Edarbi is indicated for the treatment of essential hypertension in adults.
Edurant	Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human-immunodeficiency-virus-type-1 (HIV-1) infection in antiretroviral-treatment-nave adult patients with a viral load 100,000 HIV-1 RNA copies/ml.
Efficib	For patients with type-2 diabetes mellitus.
Efient	Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST-segment-elevation myocardial infarction [UA / NSTEMI] or ST-segment- elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).
Eklira Genuair	Eklira Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Elaprase	Elaprase is indicated for the long-term treatment of patients with Hunter syndrome (mucopolysaccharidosis II, MPS II). Heterozygous females were not studied in the clinical trials.
Eliquis	Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip- or knee-replacement surgery.
ellaOne	Emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.
Elonva	Controlled ovarian stimulation in combination with a gonadotrophin-releasing-hormone antagonist for the development of multiple follicles in women participating in an assisted-reproductive-technology programme.
Emadine	Symptomatic treatment of seasonal allergic conjunctivitis.
Emend	Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years.
Emselex	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with overactive bladder syndrome.
Jakavi	Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia-vera myelofibrosis or post-essential-thrombocythaemia myelofibrosis.
Jalra	Vildagliptin is indicated in the treatment of type-2 diabetes mellitus in adults.
Janumet	For patients with type-2 diabetes mellitus.

Medicine Name	Indication
Januvia	For adult patients with type-2 diabetes mellitus, Januvia is indicated to improve glycaemic control
Jardiance	Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults.
Javlor	Javlor is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional-cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.
Jentadueto	Treatment of adult patients with type-2 diabetes mellitus.
Jetrea	Jetrea is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns.
Jevtana	Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
Jinarc	Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.
Kalydeco	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.
Karvea	Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type-2 diabetes mellitus as part of an antihypertensive medicinal product regimen.
Emtriva	Emtriva is indicated for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents.
Entacapone Orion	Entacapone is indicated as an adjunct to standard preparations of levodopa / benserazide or levodopa / carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.
Entacapone Teva	Entacapone is indicated as an adjunct to standard preparations of levodopa / benserazide or levodopa / carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.
Entyvio	Ulcerative Colitis Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. Crohn's Disease Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
Enurev Breezhaler	Enurev Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Enyglid	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise.

Medicine Name	Indication
Eperzan	Eperzan is indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control.
Epoetin Alfa Hexal	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients.
Eporatio	Treatment of symptomatic anaemia associated with chronic renal failure in adult patients.Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.
Erbitux	Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer.
Erivedge	Treatment of advanced basal-cell carcinoma.
Esbriet	Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis.
Esmya	Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
Eucreas	Eucreas is indicated in the treatment of type-2 diabetes mellitus.
Eurartesim	Eurartesim is indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, children and infants 6 months and over and weighing 5 kg or more.
Eviplera	Eviplera is indicated for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.
Evista	Evista is indicated for the treatment and prevention of osteoporosis in post-menopausal women.
Evoltra	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.
Evra	Female contraception. Evra is intended for women of fertile age. The safety and efficacy has been established in women aged 18 to 45 years.
Exelon	Symptomatic treatment of mild to moderately severe Alzheimer's dementia. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Exforge	Treatment of essential hypertension. Exforge is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.
Fabrazyme	Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase-A deficiency).
Fampyra	Fampyra is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (Expanded Disability Status Scale 4-7).
Fareston	First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.Fareston is not recommended for patients with estrogen receptor negative tumours.
Faslodex	Faslodex is indicated for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen.

Medicine Name	Indication
Fendrix	Fendrix is indicated in adolescents and adults from the age of 15 years onwards for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes for patients with renal insufficiency.
Ferriprox	Ferriprox is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.
Filgrastim Hexal	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Firazyr	Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).
Firdapse (previously Zenas)	Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.
Firmagon	Firmagon is a gonadotrophin-releasing-hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer.
Focetria	Prophylaxis of influenza caused by A (H1N1v) 2009 virus. Focetria should be used in accordance with official guidance.
Foclivia	Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.
Fortacin	Treatment of primary premature ejaculation in adult men.
Forxiga	Forxiga is indicated in adults aged 18 years and older with type-2 diabetes mellitus to improve glycaemic control.
Fosavance	Treatment of postmenopausal osteoporosis in patients at risk of vitamin-D insufficiency. Fosavance reduces the risk of vertebral and hip fractures.
Foscan	Foscan is indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy.
Fuzeon	Fuzeon is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes: protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens
Fycompa	Treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.
Galvus	Vildagliptin is indicated in the treatment of type-2 diabetes mellitus in adults.
Ganfort	Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
Gazyvaro	Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.
Giotrif	Treatment of non-small-cell lung cancer (NSCLC) with epidermal-growth-factor-receptor (EGFR) mutation(s).

Medicine Name	Indication
Glidipion (previously Pioglitazone Actavis Group)	Pioglitazone is indicated as second or third line treatment of type-2 diabetes mellitus.
Gliolan	Gliolan is indicated in adult patients for visualisation of malignant tissue during surgery for malignant glioma (World Health Organization grade III and IV).
Glubrava	Glubrava is indicated as second line treatment of type-2-diabetes-mellitus adult patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.
Glustin	Pioglitazone is indicated as second or third line treatment of type-2 diabetes mellitus.
Glybera	Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing.
Granupas (previously Para-aminosalicylic acid Lucane)	Granupas is indicated for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older.
Grastofil	Grastofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Halaven	Halavenis indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease.
HBVaxPro	HBVaxPro is indicated for active immunisation against hepatitis-B-virus infection caused by all known subtypes in individuals from birth through 15 years of age considered at risk of exposure to hepatitis-B virus.
Helicobacter Test INFAI	Helicobacter Test INFAI may be used for in vivo diagnosis of gastroduodenal Helicobacter pylori infection.
Helixate NexGen	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency).
Hepsera	Hepsera is indicated for the treatment of chronic hepatitis B in adults.
Hexacima	Primary and booster vaccination of infants and toddlers from six weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilusinfluenzae type-b (Hib).
Hexyon	Primary and booster vaccination of infants and toddlers from six weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilusinfluenzae type b (Hib).
Hirobriz Breezhaler	Hirobriz Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease.
Holoclar	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 mm^2 of undamaged limbus is required for biopsy.

Medicine Name	Indication
Hycamtin	Topotecan monotherapy is indicated for the treatment of: - patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy. - patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease.
Iasibon	Concentrate for solution for infusion:Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
Ibandronic acid Accord	Ibandronic acid is indicated in adults for − Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. − Treatment of tumour-induced hypercalcaemia with or without metastases.
Ibandronic Acid Sandoz	Ibandronic acid Sandoz is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
Ibandronic Acid Teva	Ibandronic acid 50mgIbandronic Acid Teva is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
Icandra (previously Vildagliptin / metformin hydrochloride Novartis)	Icandra is indicated in the treatment of type-2 diabetes mellitus.
Iclusig	Iclusig is indicated in adult patients with • chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
IDflu	Prophylaxis of influenza in adults up to 59 years of age, especially in those who run an increased risk of associated complications.
Ifirmacombi	Treatment of essential hypertension. This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.
Ifirmasta (previously Irbesartan Krka)	Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.
Ikervis	Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.
Ilaris	Cryopyrin-Associated Periodic Syndromes Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2years and older with body weight of 7.5kg or above.
Imbruvica	Imbruvia as a single agent is indicated for - the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). - the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Medicine Name	Indication
	- the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Imbruvica as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
Imprida	Treatment of essential hypertension. Imprida is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.
Imvanex	Active immunisation against smallpox infection and disease in adults.
Incivo	Incivo, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype-1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis).
Increlex	For the long-term treatment of growth failure in children and adolescents with severe primary insulin-like-growth-factor-1 deficiency (primary IGFD).
Incresync	Incresync is indicated as a second- or third-line treatment in adult patients aged 18years and older with type-2 diabetes mellitus.
Incruse	Indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Inductos	Inductos is indicated for single level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non operative treatment for this condition.
Infanrix Hexa	Infanrix Hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by Haemophilus influenzae type-b.
Inlyta	Inlyta is indicated for the treatment of adult patients with advanced renal-cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.
INOmax	INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated: - for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. - as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.
Intanza	Prophylaxis of influenza in adults up to 59 years of age, especially in those who run an increased risk of associated complications.
Integrilin	Integrilin is intended for use with acetylsalicylic acid and unfractionated heparin. Integrilin is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction, with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes

Medicine Name	Indication
Intelence	Intelence, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients and in antiretroviral treatment-experienced paediatric patients from 6 years of age.
Invega	Invegais indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.Invega is indicated for the treatment of schizophrenia.Invega is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder.
Invirase	Invirase is indicated for the treatment of HIV-1-infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products.
Invokana	Invokana is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control.
Irbesartan Hydrochlorothiazide Zentiva (previously Irbesartan Hydrochlorothiazide Winthrop)	Treatment of essential hypertension. This fixed-dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.
Irbesartan Teva	Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.
Irbesartan Zentiva (previously Irbesartan Winthrop)	Treatment of essential hypertension. Treatment of renal disease in patients with hypertension and type-2 diabetes mellitus as part of an antihypertensive medicinal-product regimen.
Irbesartan/Hydrochlorothiazide Teva	Treatment of essential hypertension. This fixed-dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.
Iressa	Iressa is indicated for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancerwith activating mutations of epidermal-growth-factor-receptor tyrosine kinase.
Ivemend	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults. Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
Ixiaro	Ixiaro is indicated for active immunisation against Japanese encephalitis in adults, adolescents, children and infants agedtwo months and older.
Izba	Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.
Karvezide	Treatment of essential hypertension. This fixed-dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.
Kepivance	Kepivance is indicated to decrease the incidence, duration and severity of oral mucositis in adult patients with haematological malignancies receiving myeloablative radiochemotherapy associated with a high incidence of severe mucositis.

Medicine Name	Indication
Ketek	In patients of 18 years and older: • Community-acquired pneumonia, mild or moderate. • When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin: - Acute exacerbation of chronic bronchitis, - Acute sinusitis In patients of 12 years and older: • Tonsillitis/pharyngitis caused by Streptococcus pyogenes, as an alternative when beta lactam antibiotics are not appropriate in countries/regions with a significant prevalence of macrolide resistant S. pyogenes, when mediated by ermTR or mefA.
Kineret	Kineret is indicated for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in adults with an inadequate response to methotrexate alone.
Kinzalkomb	Treatment of essential hypertension.
Kinzalmono (previously Telmisartan Boehringer Ingelheim Pharma KG)	Treatment of essential hypertension in adults.
Kogenate Bayer	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.
Kolbam (previously Cholic Acid FGK)	Kolbam is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacylCoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.
Komboglyze	Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets. Komboglyze is also indicated in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control. Komboglyze is also indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when the maximally tolerated dose of both metformin and the sulphonylurea does not provide adequate glycaemic control.
Krystexxa	Krystexxa is indicated for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated
Kuvan	Kuvan is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.

Medicine Name	Indication
Latuda	Treatment of schizophrenia in adults aged 18 years and over.
Laventair	Laventair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Leganto	Leganto is indicated for the symptomatic treatment of moderate to severe idiopathic restless-legs syndrome in adults.
LeukoScan	LeukoScan is indicated for diagnostic imaging for determining the location and extent of infection/inflammation in bone in patients with suspected osteomyelitis.
Levitra	Treatment of erectile dysfunction in adult men.
Lojuxta	Lojuxta is indicated as an adjunct to a lowfat diet and other lipidlowering medicinal products with or without low-density-lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).
Lonquex	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
Lucentis	Lucentis is indicated in adults for: - The treatment of neovascular (wet) age-related macular degeneration (AMD) - The treatment of visual impairment due to choroidal neovascularisation (CNV) - The treatment of visual impairment due to diabetic macular oedema (DME) - The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).
Lumigan	Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers).
Luminity	Luminity is an ultrasound contrast-enhancing agent for use in patients in whom non-contrast echocardiography was suboptimal.
Luveris	Luveris in association with a follicle-stimulating-hormone (FSH) preparation is recommended for the stimulation of follicular development in women with severe luteinising-hormone (LH) and FSH deficiency.
Lymphoseek	Radiolabelled Lymphoseek is indicated for imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity.
Lynparza	Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.
Lysodren	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma..
Lyxumia	Lyxumia is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control.
M-M-RVAXPRO	M-M-RVAXPRO is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months or older.
Macugen	Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).
Marixino (previously Maruxa)	Treatment of patients with moderate to severe Alzheimers disease.

Medicine Name	Indication
Mekinist	Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Memantine Accord	Treatment of patients with moderate to severe Alzheimers disease.
Memantine LEK	Treatment of patients with moderate to severe Alzheimers disease.
Memantine Merz	Treatment of patients with moderate to severe Alzheimers disease.
Memantine Mylan	Treatment of patients with moderate to severe Alzheimers disease.
Memantine ratiopharm	Treatment of patients with moderate to severe Alzheimers disease
Mepact	Mepact is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with postoperative multi-agent chemotherapy.
Methylthioninium chloride Proveblue	Acute symptomatic treatment of medicinal and chemical product-induced methaemoglobinaemia.Methylthioninium chloride Proveblue is indicated in adults, children and adolescents (aged 0 to 17 years old).
Micardis	Treatment of essential hypertension in adults.
MicardisPlus	Treatment of essential hypertension.
Mirapexin	Mirapexin is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa.
Mircera	Treatment of symptomatic anaemia associated with chronic kidney disease (CKD).
Moventig	Treatment of opioid-induced constipation (OIC) in adult patients.
Mozobil	Mozobil is indicated in combination with granulocyte-colony-stimulating factor to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.
Multaq	Multaq is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).
Mycamine	Mycamine is indicated for: Adults, adolescents ≥ 16 years of age and elderly: - Treatment of invasive candidiasis. - Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate. - Prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µl) for 10 or more days. Children (including neonates) and adolescents < 16 years of age: - Treatment of invasive candidiasis. - Prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µl) for 10 or more days.
Myozyme	Myozyme is indicated for long-term enzyme-replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid--glucosidase deficiency).
Naglazyme	Naglazyme is indicated for long-term enzyme-replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine-4-sulfatase deficiency; Maroteaux-Lamy syndrome).
Nemdatine	Treatment of patients with moderate to severe Alzheimers disease.

Medicine Name	Indication
Neoclarityn	Neoclarityn is indicated for the relief of symptoms associated with: allergic rhinitis urticaria.
NeoRecormon	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients. Treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy.
Neulasta	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
Neupro	Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or in combination with levodopa.
Neuraceq	Neuraceq is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of amyloid neuritic plaque density in the brains of adult patients with cognitive impairment.
NeuroBloc	NeuroBloc is indicated for the treatment of cervical dystonia (torticollis).
Nevanac	Nevanac is indicated for: prevention and treatment of postoperative pain and inflammation associated with cataract surgery; reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.
Nexavar	Hepatocellular carcinoma Renal cell carcinoma
Nexium Control	Nexium Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.
NexoBrid	NexoBrid is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns.
Nimvastid	Symptomatic treatment of mild to moderately severe Alzheimer's dementia.Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Nivestim	Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Nonafact	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).
Norvir	Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1-infected patients (adults and children oftwo years of age and older).
NovoEight	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Novoeight can be used for all age groups.
NovoNorm	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise.
NovoThirteen	Long-term prophylactic treatment of bleeding in adult and paediatric patients 6 years and above with congenital factor-XIII-A-subunit deficiency.
Nuedexta	Nuedexta is indicated for the symptomatic treatment of pseudobulbar affect (PBA) in adults (see section 4.4). Efficacy has only been studied in patients with underlying amyotrophic lateral sclerosis or multiple sclerosis.
Nulojix	Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejectionin adults receiving a renal transplant.

Medicine Name	Indication
NutropinAq	Paediatric population - Long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion. - Long-term treatment of girls from 2 years old with growth failure associated with Turner syndrome. - Treatment of prepubertal children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Adult population - Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset etiology. Growth hormone deficiency should be confirmed appropriately prior to treatment.
Nuwiq	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
Ofev	Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).
Olysio	Olysio is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients.
Omnitrope	Infants, children and adolescents: - Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD). - Growth disturbance associated with Turner syndrome. - Growth disturbance associated with chronic renal insufficiency. - Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted height SDS < -1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later. - Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. Adults: - Replacement therapy in adults with pronounced growth hormone deficiency.
Onbrez Breezhaler	Onbrez Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease.
Onglyza	Add-on combination therapyOnglyza is indicated in adult patients aged 18 years and older with type-2 diabetes mellitus to improve glycaemic control.
Opatanol	Treatment of ocular signs and symptoms of seasonal allergic conjunctivitis.
Opgenra	Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed or is contra-indicated.
Oprymea	Oprymea is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa.
Opsumit	Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.
Optaflu	Prophylaxis of influenza for adults, especially in those who run an increased risk of associated complications.
Optimark	Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver.

Medicine Name	Indication
Optison	Optison is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers, enhance left-ventricular endocardial border delineation with resulting improvement in wall motion visualisation.
Optruma	Optruma is indicated for the treatment and prevention of osteoporosis in post-menopausal women.
Orbactiv	Orbactiv is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Orencia	Rheumatoid arthritis Polyarticular juvenile idiopathic arthritis
Orfadin	Treatment of patients with confirmed diagnosis of hereditary tyrosinaemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.
Orgalutran	The prevention of premature luteinising-hormonesurges in women undergoing controlled ovarian hyperstimulationfor assisted reproduction techniques.
Orphacol	Orphacol is indicated for the treatment of inborn errors in primary bile-acid synthesis due to 3-hydroxy-5-C27-steroid oxidoreductase deficiency or 4-3-oxosteroid-5-reductase deficiency.
Osigraft	Treatment of nonunion of tibia of at least 9 month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or use of autograft is unfeasible.
Oslif Breezhaler	Oslif Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease.
Osseor	Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures. Treatment of severe osteoporosis in adult men at increased risk of fracture.
Otezla	Psoriatic arthritis Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Psoriasis Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).
Ovitrelle	Ovitrelle is indicated in the treatment of: • Adult women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF): Ovitrelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth, • Anovulatory or oligo-ovulatory adult women: Ovitrelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory women after stimulation of follicular growth.
Paglitaz	Pioglitazone is indicated as second or third line treatment of type2 diabetes mellitus.
Paliperidone Janssen	Paliperidone Janssen is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.
Pandemic Influenza Vaccine H5N1 Baxter AG	Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

Medicine Name	Indication
Pandemrix	Prophylaxis of influenza caused by A (H1N1)v 2009 virus.
Panretin	Panretin gel is indicated for the topical treatment of cutaneous lesions in patients with acquired-immune-deficiency-syndrome (AIDS)-related Kaposi's sarcoma (KS).
Pantecta Control	Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
Pantoloc Control	Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
Pantozol Control	Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
Pegasys	Chronic hepatitis B Chronic hepatitis C
PegIntron	Treatment of chronic hepatitis C
Perjeta	Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.
Peyona (previously Nymusa)	Treatment of primary apnoea of premature newborns.
Picato	Picato is indicated for the cutaneous treatment of nonhyperkeratotic, nonhypertrophic actinic keratosis in adults.
Pioglitazone Accord	Pioglitazone is indicated in the treatment of type-2 diabetes mellitus.
Pioglitazone Actavis	Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus.
Pioglitazone Teva	Pioglitazone is indicated in the treatment of type 2 diabetes mellitus.
Pioglitazone Teva Pharma	Pioglitazone is indicated in the treatment of type 2 diabetes mellitus.
Pixuvri	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL).
Plegridy	Treatment of relapsing remitting multiple sclerosis in adult patients.
Potactasol	Topotecan monotherapy is indicated for the treatment of: - patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy - patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease.
Pradaxa	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
Pramipexole Accord	Pramipexole Accord is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa.
Pramipexole Teva	Pramipexole Teva is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa.
Prandin	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)).

Medicine Name	Indication
Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics	Active immunisation against H5N1 subtype of Influenza A virus.
Prepandrix	Active immunisation against H5N1 subtype of influenza-A virus.
Prezista	Prezista film-coated tablets co-administered with low-dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human-immunodeficiency-virus (HIV-1) infection.
Prialt	Ziconotide is indicated for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.
Pritor	Treatment of essential hypertension in adults.
PritorPlus	Treatment of essential hypertension.
Procoralan	Treatment of coronary-artery disease.
Procysbi	Procysbi is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients.
Prolia	Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.
Prometax	Symptomatic treatment of mild to moderately severe Alzheimer's dementia. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
ProQuad	ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in individuals from 12 months of age.
Protelos	Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures. Treatment of severe osteoporosis in adult men at increased risk of fracture.
Pylobactell	For in vivo diagnosis of gastroduodenal Helicobacter pylori (H. pylori) infection.
Quadramet	Quadramet is indicated for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases which take up technetium [99mTc]-labelled biphosphonates on bone scan.
Qutenza	Qutenza is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.
Raloxifene Teva	Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women.
Ranexa (previously Latixa)	Ranexa is indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and / or calcium antagonists).
Rapilysin	Rapilysin is indicated for the thrombolytic treatment of suspected myocardial infarctionwith persistent ST elevation or recent left bundle branch block within 12 hours after the onset of acute-myocardial-infarction symptoms.
Rapiscan	Rapiscan is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.
Rasilamlo	Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

Medicine Name	Indication
Rasilez	Treatment of essential hypertension.
Rasilez HCT	Treatment of essential hypertension in adults.
Ratiograstim	Ratiograstim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Rebetol	Rebetol is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. Rebetol is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) for paediatric patients (children 3 years of age and older and adolescents) not previously treated and without liver decompensation.
ReFacto AF	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency).
Relistor	Treatment of opioid-induced constipation in advanced-illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.
Removab	Removab is indicated for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.
Renagel	Renagel is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
Renvela	Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
Repaglinide Accord	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)).
Repaglinide Krka	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)).
Repaglinide Teva	Repaglinide is indicated in patients with type-2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)).
Replagal	Replagal is indicated for long-term enzyme-replacement therapy in patients with a confirmed diagnosis of Fabry disease (-galactosidase-A deficiency).
Resolor	Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.
Retacrit	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients.
Revestive	Revestive is indicated for the treatment of adult patients with short-bowel syndrome.
Revolade	Revolade is indicated for adult chronic-immune (idiopathic)-thrombocytopenic-purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
Reyataz	Reyataz capsules, co-administered with low-dose ritonavir, are indicated for the treatment of HIV1-infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.
Rezolsta	Rezolsta, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus 1 (HIV 1) infection in adults aged 18 years or older.
Ribavirin Mylan (previously Ribavirin Three Rivers)	Ribavirin Mylan is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with interferon alfa-2b (adults, children (three years of age and older) and adolescents).

Medicine Name	Indication
Ribavirin Teva	Ribavirin Teva is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults, children 3 years of age and older and adolescents and must only be used as part of a combination regimen with interferon alfa-2b.
Ribavirin Teva Pharma B.V.	Ribavirin Teva Pharma B.V. is indicated for the treatment of chronic hepatitis-C-virus (HCV) infection in adults, children three years of age or older and adolescents and must only be used as part of a combination regimen with interferon alfa-2b.
Rienso	Rienso is indicated for the intravenous treatment of iron-deficiency anaemia in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests.
Ristaben	For adult patients with type-2 diabetes mellitus, Ristaben is indicated to improve glycaemic control.
Ristempa	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy.
Ristfor	For patients with type-2 diabetes mellitus.
Rivastigmine 1 A Pharma	Symptomatic treatment of mild to moderately severe Alzheimer's dementia.Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Rivastigmine Actavis	Symptomatic treatment of mild to moderately severe Alzheimer's dementia. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Rivastigmine Hexal	Symptomatic treatment of mild to moderately severe Alzheimer's dementia.Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Rivastigmine Sandoz	Symptomatic treatment of mild to moderately severe Alzheimer's dementia.Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Rixubis	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).
RoActemra	RoActemra, in combination with methotrexate (MTX), is indicated for • the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX. • the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
Rotarix	Rotarix is indicated for the active immunisation of infants aged 6 to 24 weeks for prevention of gastroenteritis due to rotavirus infection.
RotaTeq	RotaTeq is indicated for the active immunisation of infants from the age ofsix weeks to 32 weeks for prevention of gastroenteritis due to rotavirus infection.
Ruconest	Ruconest is indicated for treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1-esterase-inhibitor deficiency.
Sabervel	Sabervel is indicated in adults for the treatment of essential hypertension. It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.
Samsca	Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic-hormone secretion (SIADH).

Medicine Name	Indication
Sancuso	Prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy, with or without cisplatin, for up tofive consecutive days.
Savene	Savene is indicated for the treatment of anthracycline extravasation.
Saxenda	Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of 30 kg/m (obese), or 27 kg/m to 30 kg/m (overweight).
Scenesse	Prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
Scintimun	This medicinal product is for diagnostic use only and the approved indication is scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/ infection in peripheral bone in adults.
Sebivo	Sebivo is indicated for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation.
Seebri Breezhaler	Seebri Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Selincro	Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking-risk level, without physical withdrawal symptoms and who do not require immediate detoxification.
Senshio	Senshio is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy.
Sevelamer carbonate Zentiva	Sevelamer carbonate Zentiva is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
Sifrol	Sifrolis indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa)or in combination with levodopa.
Signifor	Signifor is indicated for the treatment of adult patients with Cushings disease for whom surgery is not an option or for whom surgery has failed. Signifor is indicated for the treatment of adult patients with acromegaly for whom surgery is not an option.
Siklos	Siklos is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic sickle-cell syndrome.
Silapo	Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients.
Silodyx	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).
Simbrinza	Decrease of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.
Simponi	Rheumatoid arthritis (RA) Psoriatic arthritis (PsA) Axial spondyloarthritis Ulcerative colitis (UC)
Sirturo	Indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Medicine Name	Indication
Sivextro	Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Soliris	Soliris is indicated in adults and children for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH).
Somac Control	Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.
Somatropin Biopartners	Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth-hormone deficiency (GHD).
Sonata	Sonata is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress.
SonoVue	SonoVue is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal-to-noise ratio.
Sovaldi	Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.
Spedra	Treatment of erectile dysfunction in adult men.
Starlix	Nateglinide is indicated for combination therapy with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.
Stelara	Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.
Stivarga	Stivarga is indicated for the treatment of adult patients with: - metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. - unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
Stribild	Stribild is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild.
Suboxone	Substitution treatment for opioid-drug dependence, within a framework of medical, social and psychological treatment.
Sycrest	Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.
Sylvant	Sylvant is indicated for the treatment of adult patients with multicentric Castlemans disease (MCD who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
Synjardy	Synjardy is indicated in adults aged 18years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.
Tadalafil Mylan	Treatment of erectile dysfunction in adult males. In order for tadalafil to be effective, sexual stimulation is required..
Tafinlar	Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Tandemact	Tandemact is indicated for the treatment of patients with type-2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride.

Medicine Name	Indication
Tasermity	Tasermity is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
Tasmar	Tasmar is indicated in combination with levodopa / benserazide or levodopa / carbidopa for use in patients with levodopa-responsive idiopathic Parkinsons disease and motor fluctuations.
Telmisartan Actavis	Treatment of essential hypertension in adults.
Telmisartan Teva	Treatment of essential hypertension in adults.
Telmisartan Teva Pharma	Treatment of essential hypertension in adults.
Telzir	Telzir in combination with low-dose ritonavir is indicated for the treatment of human-immunodeficiency-virus-type-1-infected adults, adolescents and children ofsix years and above in combination with other antiretroviral medicinal products.
Tepadina	Tepadina is indicated, in combination with other chemotherapy medicinal products: • with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients; • when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.
Tesavel	For patients with type-2 diabetes mellitus, Tesavel is indicated to improve glycaemic control.
Tevagrastim	Tevagrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Teysuno	Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.
Thymanax	Treatment of major depressive episodes in adults.
Thyrogen	Thyrogen is indicated for use with serum thyroglobulin (Tg) testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone-suppression therapy.
Tivicay	Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.
Tolucombi	Treatment of essential hypertension.
Tolura	Treatment of essential hypertension in adults.
Topotecan Actavis	Topotecan monotherapy is indicated for the treatment of patients with relapsed small cell lung cancer [SCLC] for whom re-treatment with the first-line regimen is not considered appropriate.
Topotecan Hospira	Topotecan monotherapy is indicated for the treatment of patients with relapsed small-cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.
Topotecan Teva	Topotecan monotherapy is indicated for the treatment of: - patients with metastatic carcinoma of the ovary after failure of first line or subsequent therapy. - patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination.
Torisel	Renal-cell carcinoma Mantle-cell lymphoma

Medicine Name	Indication
Tovanor Breezhaler	Tovanor Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Toviaz	Treatment of the symptoms (increased urinary frequency and / or urgency and / or urgency incontinence) that may occur in patients with overactive-bladder syndrome.
Trajenta	Trajenta is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control.
Travatan	Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.
Trisenox	Trisenox is indicated for induction of remission and consolidation in adult patients with relapsed / refractory acute promyelocytic leukaemia (APL).
Trobalt	Trobalt is indicated as adjunctive treatment of drug-resistant partial-onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy.
Trulicity	Trulicity is indicated in adults with type-2 diabetes mellitus to improve glycaemic control.
Truvada	Truvada is a fixed dose combination of emtricitabine and tenofovir disoproxil fumarate. It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults.
Twinrix Adult	Twinrix Adult is indicated for use in non immune adults and adolescents 16 years of age and above who are at risk of both hepatitis A and hepatitis B infection.
Twinrix Paediatric	Twinrix Paediatric is indicated for use in non-immune infants, children and adolescents fromone year up to and including 15 years who are at risk of both hepatitis-A and hepatitis-B infection.
Twynsta	Treatment of essential hypertension in adults.
Tybost	Tybost is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human-immunodeficiency-virus-1 (HIV-1)-infected adults.
Tyverb	Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2).
Ultibro Breezhaler	Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Urorec	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).
Valdoxan	Treatment of major depressive episodes in adults.
Vaniqa	Treatment of facial hirsutism in women.
Vantavo (previously Alendronate sodium and colecalciferol, MSD)	Treatment of postmenopausal osteoporosis in patients at risk of vitamin-D insufficiency.
Vectibix	Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC).
Vedrop	Vedrop is indicated in vitamin-E deficiency due to digestive malabsorption in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis, from birth (in term newborns) to 16 or 18 years of age.
Velmetia	For patients with type-2 diabetes mellitus.
Velphoro	Velphoro is indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD).
Vepacel	Active immunisation against H5N1 subtype of influenza A virus.

Medicine Name	Indication
Vibativ	Vibativ is indicated for the treatment of adults with nosocomial pneumoniaincluding ventilator-associated pneumonia, known or suspected to be caused by methicillin-resistant Staphylococcus aureus (MRSA).
Victoza	Victoza is indicated for treatment of adults with type-2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin.
Victrelis	Victrelis is indicated for the treatment of chronic hepatitis-C (CHC) genotype-1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease.
Vimizim	Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.
Vimpat	Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.
Vipdomet	Vipdomet is indicated in the treatment of adult patients aged 18 years and older with type-2 diabetes mellitus.
Vipidia	Vipidia is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin.
ViraferonPeg	ViraferonPeg in combination with ribavirin and boceprevir (tritherapy) is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adult patients (18 years of age and older) with compensated liver disease who are previously untreated or who have failed previous therapy.
Visudyne	Visudyne is indicated for the treatment of - adults with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) or - adults with subfoveal choroidal neovascularisation secondary to pathological myopia.
Vitekta	Vitekta co-administered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir.
Vivanza	Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
Vizamyl	Vizamyl is a radiopharmaceutical medicinal product indicated for Positron Emission Tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment.
Vokanamet	Vokanamet is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.
Volibris	Volibris is indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as World Health Organization functional class II and III, to improve exercise capacity.
Votrient	Renal-cell carcinoma (RCC) Soft-tissue sarcoma (STS)
Vpriv	Vpriv is indicated for long-term enzyme-replacement therapy (ERT) in patients with type-1 Gaucher disease.
Vyndaqel	Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage-1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

Medicine Name	Indication
Xadago	Xadago is indicated for the treatment of adult patients with idiopathic Parkinsons disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.
Xalkori	Xalkori is indicated for the treatment of adults with previously treated anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).
Xelevia	For adult patients with type-2 diabetes mellitus, Xelevia is indicated to improve glycaemic control.
Xeloda	Xeloda is indicated for the treatment of: - for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. - metastatic colorectal cancer. - first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. - in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. - as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Xenical	Xenical is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m^2, or overweight patients (BMI 28 kg/m^2) with associated risk factors.
Xeplion	Xeplion is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.
Xeristar	Treatment of major depressive disorder. Treatment of diabetic peripheral neuropathic pain. Treatment of generalised anxiety disorder.
Xgeva	Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.
Xiapex	Xiapex is indicated for the treatment of Dupuytrens contracture in adult patients with a palpable cord.
Xigduo	Xigduo is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.
Xiliarx	Vildagliptin is indicated in the treatment of type-2 diabetes mellitus in adults:as monotherapyin patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance;as dual oral
Xofigo	Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.
Xoterna Breezhaler	Xoterna Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Xultophy	Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products.
Xydalba	Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.
Yellox	Treatment of postoperative ocular inflammation following cataract extraction in adults.

Medicine Name	Indication
Yentreve	Yentreve is indicated for women for the treatment of moderate to severe stress urinary incontinence (SUI).
Yervoy	Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
Yondelis	Yondelis is indicated for the treatment of patients with advanced soft-tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.
Ytracis	To be used only for the radiolabelling of carrier molecules which have been specifically developed and authorised for radiolabelling with this radionuclide.
Yttriga	To be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.
Zaltrap	Treatment of metastatic colorectal cancer (MCRC).
Zarzio	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy.
Zavesca	Zavesca is indicated for the oral treatment of adult patients with mild to moderate type-1 Gaucher disease.
Zebinix	Zebinix is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.
Zelboraf	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.
Zerit	Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-infected adult patients and paediatric patients (over the age ofthree months) only when other antiretrovirals can not be used.
Zevalin	[90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma.
Zinforo	Zinforo is indicated in adults for the treatment of the following infections: complicated skin and soft tissue infections (cSSTI); community-acquired pneumonia (CAP).
Zoely	Oral contraception
Zomarist	Zomarist is indicated in the treatment of type-2 diabetes mellitus.
Zontivity	Zontivity, co-administered with acetylsalicylic acid (ASA) and, where appropriate, clopidogrel, is indicated for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction (MI).
Zostavax	Zostavax is indicated for prevention of herpes zoster ('zoster' or shingles) and herpes-zoster-related post-herpetic neuralgia.
Zyclara	Zyclara is indicated for the topical treatment of clinically typical, non-hyperkeratotic, non-hypertrophic, visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults.
Zydelig	Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).
Zykadia	Treatment of anaplastic lymphomakinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer.
Zytiga	Treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen-deprivation therapy in whom chemotherapy is not yet clinically indicated.

APPENDIX 8

Interviews

Interview with Ms Helen Vella Licensing Director, Malta Medicines Authority

Date: 06/02/2017

Discussion points:

1. What is the role of the Malta Medicines Authority?
2. Do you agree that there is a current imbalance within the pharmaceutical system, which poses challenges to our public health systems with regards to CAPs including innovative medicines?
3. What are the challenges with registration and access of CAPs including innovative medicines in Malta?
4. What initiatives are being taken to increase registration and access of innovative medicines?
5. Do you think that EU collaboration especially with other small markets is the way forward?

Summary of Discussion:

The interpretation of the discussion expressed in this summary is the sole responsibility of the researcher and does not necessarily reflect the exact views of the interviewee.

The MMA is the National Competent Authority in Malta for medicinal products and pharmaceutical activities and is committed to protect and enhance public health through its regulatory role.

The MMA works very closely with the European Medicines Agency and provides the local scientific expertise for assessing centralised and European procedures. The MMA agrees that there is a current imbalance within the pharmaceutical system and that member states should join forces and take action on this issue. Health regulators should discuss more closely with HTA bodies on the issues of work-sharing and data sharing in order to strengthen their collaboration. There is scope for closer, strategic collaboration between all member states at EU level, not only small member states. Howver, there should always be strenghthened collaboration between national entities in order to ensure a sustainable national pharmaceutical system and National Health Service. There should be further insight into the working of the pharmaceutical regulatory system and how it impacts accessibility of medicines.

Lack of accessibility in Malta related to marketing authorisation requirements could be due to:

- Medicines not authorised in Malta, for example Malta is not included as a concerned member state (CMS)

- Medicines authorised nationally or centrally but not marketed, for example, too few patients
- Medicines being authorised and marketed but unavailable due to shortages or supply chain issues, e.g. liothyronine 20mcg tablets, pilocarpine 5mg tablets

The number of medicines authorised by the MMA amounts to around 5,200. Increase in the number of authorisations has been seen following various initiatives taken up by the Authority in order to increase the access and availability of medicines on the market.

The MMA understands that access to medicines is a priority and way before the start of the EU Medicines Agency Network Strategy, in November 2014 the MMA expanded proactively its activities with the setting up of the Medicines Intelligence and Access Unit. This initiative was a very important step to the MMA, to better communicate the overall objective of safeguarding human health. The Medicines Intelligence and Access Unit is responsible to manage a proactive and targeted approach taking into account the expectations and needs of both patients, health care professionals and other stakeholders.

In collaboration with the Malta Competition and Consumer Affairs Authority (MCCAA), the Medicines Intelligence and Access Unit is on an ongoing process of dialogue with stakeholders in the pharmaceutical sector to ensure that the medicines remain at an affordable price for the patients, and the public will also have access to essential medicines with a reasonable price when compared to other countries. This is leading to a reduction in prices of medicines for the benefit of consumers which to date has led to 143 medicines price reduction.

During the ongoing information campaign Mediċini: Għażla Aħjar Għalik', consumers are being informed about the choice of medicines available on the local market and the importance of discussing these choices with healthcare professionals. The MMA is continuously updating lists of generic medicines which have been recently authorised and is comparing the prices of these medicines with the originators and other generics so that the consumer can use such information to decide the best treatment option. All of these generic medicines have been assessed by the MMA to ensure that all medicines conform to the established standards of quality, safety and efficacy.

Since 2009, the MMA has set a process for scientific advice and protocol assistance requests. The applications accepted are for generic medicinal products in line with the MMA's RMS activity. In 2014, one scientific advice request has been submitted to the MMA. To facilitate the process for industry and ensure consistency at European Level, the advice was given jointly with the Austrian Medicines Agency (AGES). Officers from the MMA participated and delivered their scientific evaluations in Vienna to an applicant developing a medicinal product in the area of Duchenne's Muscular Dystrophy, an orphan disease. In 2016, Malta was the Rapporteur evaluating a type II variation of this product which has a conditional centralised marketing authorisation.

During 2016, the MMA continued with activities towards national and European procedures for the registration of new medicinal products. The overall number of these pre-authorisation procedures in 2016 was 39. It is planned to continue to increase the numbers of these procedures as Malta focuses to attract more applicants to choose it as a RMS.

Interview with Ms Antonia Formosa Director, Directorate of Pharmaceutical Affairs

Date: 09/02/2017

Discussion points:

1. What is the role of the DPA?
2. Do you agree that there is a current imbalance within the pharmaceutical system, which poses challenges to our public health systems with regards to CAPs including innovative medicines?
3. To what extent is the current pricing model and its impact on our health care systems sustainable.
4. What initiatives are being taken to increase access to innovative medicines through the NHS?
5. What happens when a patient needs treatment, e.g. an orphan medicine, which is not in the formulary?
6. What are your views on joint HTA assessments with other Member States? Has DPA done any joint assessments? Are the HTA assessments shared with other entities or Member States?
7. What is the role of the GFLAC? How does the role of the Advisory Committee on Health Benefits differ?
8. What is the role of the Exceptional Medicines Treatment Policy? Who is eligible and for what diseases? Are orphan medicines not included in the formulary provided through this policy?
9. Do you think that EU collaboration especially with other small markets is the way forward?

Summary of Discussion:

The interpretation of the discussion expressed in this summary is the sole responsibility of the researcher and does not necessarily reflect the exact views of the interviewee.

The DPA holds a challenging and central position within the Maltese national health system as it strives to work within a tight balance between safeguarding public health and securing patient access to safe and effective good quality medicines yet in a manner that is equitable and sustainable. DPA has the mission of developing and implementing equitable and sustainable Government pharmaceutical policies. It promotes excellence in patient care through assuring safe, rational and cost-effective use of medicines.

Major legislative changes occurred in 2012 with the addition of 41 conditions. This was followed by two minor changes in 2014 and 2015, with addition of another 3

conditions. These legislative changes brought about an increase in access to medicines to a wider population.

A Health Act was issued in 2013 the scope to establish and ensure a health system based on the principles of accessibility, quality and sustainability by regulating the entitlement to, and the quality of, healthcare services in Malta, consolidating and reforming the Government structures and entities responsible for health and by providing for the rights of patients. This enabled the establishment of committees and sub-committees such as the Advisory Committee on Healthcare Benefits (ACHCB) and Government Formulary List Advisory Committee (GFLAC). These committees have the responsibility to recommend the healthcare benefits to be provided directly or indirectly.

Availability of medicines within the Government Health System Regulations is regulated by Legal Notice 58 of 2009 for the promotion of public health by ensuring the availability of adequate supplies of medicinal products at a reasonable cost in Government Health Services. This includes regulations on introduction of new medicines on the Government Formulary List.

With regards to pricing, pricing computations are performed within DPA to assist and serve as a reference price control during the procurement process of all the medicines. Pricing computations also serve as guidance for HTA reviews of new medicines proposed for introduction onto the GFL. Research of medicine prices is conducted from a basket of EU countries falling within the bracket of +/-20 percentage points of Malta's GDP per capita in Purchasing Power Standards (PPS) using EUROSTAT figures, together with the UK price. Pricing of innovative medicines is becoming a challenge for national health systems due to the high prices being imposed.

The exceptional medicinal treatment policy was an initiative taken up to provide access to evidence-based, cost-effective medicinal treatment for individuals with an exceptional need for treatment not currently provided by the national health system. Thos policy provides a means for the consideration of pharmaceutical funding for patients in exceptional circumstances who would otherwise not have access to needed medication. Access to medication always aims to decrease disease morbidity, would eventually translate into a diminished use of other health state resources such a decreased hospital admissions/length of stay. Accessibility to orphan medicines was discussed and if the treatment falls within the protocol of the exceptional medicinal treatment policy, this is supplied to the patient for free through the government. However, if the criteria are not fulfilled, patients are referred to the Community Chest Fund which is a charitable foundation, regulated by the civil code, under the auspices of The President of Malta. The aim of the institution is to help philanthropic institutions and more importantly, the individuals with different needs.
It was agreed that EU collaboration is one of the ways to overcome these challenges of affordability of medicines especially for a small member state such as Malta. DPA

participates in various EU projects involving sharing of information related to pharmaceutical policies, pricing and reimbursement of medicine, between the participating member states. Collaborations are aimed for continual improvement of various aspects of Pharmaceutical Policy in Malta. Collaborations include Collaborations include the: HTA Network; European Network for Health Technology; Assessment (EUnetHTA); The Pharmaceutical Pricing and Reimbursement Information (PPRI) network; and The Network of Competent Authorities for Pricing and Reimbursement (CAPR).

Being part of the EUnetHTA, DPA one of the initiatives being taken is joint HTA assessment. A joint assessment is a structured information tool for rapid or full/comprehensive HTAs which is the output of joint production in which 2 or more countries and/or organisations work together to prepare shared products or agreed outcomes. In the long term, this avoids duplication of work and of utmost importance, sharing of information. The European Commission is also exploring options for a new and sustainable mechanism for HTA in Europe after 2020.

Data and the overall evidence available at authorisation stage is often insufficient to accurately estimate the clinical and cost-effectiveness of a drug in clinical practice or its budget impact in real life. Formal arrangements between HTA bodies and manufacturers with the aim of sharing the financial risk due to uncertainty surrounding the introduction of new technologies have been developed and introduced in order to enable access to new medicines. These agreements can take different forms, including price-volume agreements (PVAs), outcome guarantee, and disease management programmes. A variety of names have been used to describe these schemes (e.g. risk-sharing agreements (RSAs), performance-based agreements (PBAs), patient access schemes (PAS), etc.), which have been recently summarised with the concept of ‘managed entry agreements (MEAs)’. These are being considered and implemented by some of the member states, for example The Netherlands. A disadvantage of these agreements includes the lack of transparency where the price set for one member state is not necessary the same as the price for another member states. Some member states are also moving to signing joint managed entry agreements. Malta has not yet taken part in these formal agreements. A robust data system with state of the art information technology systems should be in place to be able to gather the correct information as prove of evidence. Registers should be implemented to compile ‘real-world data’ which is required for these innovative medicines and technologies.

Interview with Ms Alison Anastasi, Assistant Director, Central Procurement and Supplies Unit

Date: 09/02/2017

Discussion points:

1. What is the role of CPSU?
2. Do you agree that there is a current imbalance within the pharmaceutical system, which poses challenges to our public health systems with regards to CAPs including innovative medicines?
3. To what extent is the current pricing model and its impact on our health care systems sustainable.
4. What initiatives are being taken to increase access to innovative medicines through the NHS?
5. What happens when a patient needs treatment, e.g. an orphan medicine, which is not in the formulary?
6. What is the role of the ERU? How do you classify emergency?
7. What challenges are encountered during the procurement of innovative medicines?
8. What are your views on joint procurement with other Member States?
9. Do you think that innovative risk-sharing agreements are the way forward?
10. What is being done in order to set up patient registries, which would support the implementation of such agreements. Who will be managing these patient registries?
11. Do you think that there should price control on tendered products, e.g. quoted price should not be higher than the reference price?

Summary of Discussion:

The interpretation of the discussion expressed in this summary is the sole responsibility of the researcher and does not necessarily reflect the exact views of the interviewee.

The Central Procurement and Supplies Unit (CPSU) manages the procurement and supply of materials, works and/or services across the Government Healthcare Services. This organisation acquires quality materials, works and services at the lowest price; gives timely and effective support to ensure that the requirements of the Government Healthcare services to the community are met; provides potential suppliers with equal consideration of their products and services; and instils public confidence that contracts are awarded in full transparent, equitable and economical manner.

The annual expenditure budget on health procurement is €350 million which equates to around €835 per citizen. The annual expenditure budget on treatment is €97 million where €60 million are spent to procure 300 million medicines.

Apart from the challenges of high prices of medicines especially innovative medicines, there are also a number of challenges for Malta being a small member state. Malta is highly dependent on importation. Due to its size and geographical position, transportation to Malta through importation from other countries is a factor for higher prices. Malta also has a small domestic market especially with regards to hospital items and exceptional medicines. This leads to accessibility problems. There is also no competition for the low volumes required since neither the Marketing Authorisation Holder tenders for the medicine. The National Health Service is dependent Dependence on a narrower range of products when compared to other markets. Sometimes this may be due to registration issues or language barrier which would require over-labelling.

To overcome some of these challenges, CPSU introduced a series of reforms to procurement practices in Malta. The main objective is to place the patient care at the centre of the activities. Improving practises has resulted in the eradication of stock-outs and strengthening of the partnership relationship with industry has limited the risks and wastages on both sides. The annual forecast of needs of all hospitals is posted on the CPSU portal and the annual Supplier Conference was setup amongst the key stakeholders to share ideas about how to improve the process. The financial terms and protocols were also improved.

CPSU has a valid wholesale dealer licence where the unit can procure the medicines which are not available, at preferably cheaper prices. An Emergency Response Unit was also setup to mitigate abrupt fluctuations in demand. This unit is responsible to finds ways of procuring medicines which are either out of stock or there are no bidders for the tender and there is immediate demand for the medicine. Regulatory pathways such as 126(a) authorisations, use of medicines on a named patient basis and procurement of medicines approved as exceptional cases in line with Article 20 (1) of the Medicines Act, 2003, are used.

Other initiatives which were taken up include:

- Product registration can take place after the award is announced
- No penalties are imposed on the supplier as long as there is stock available
- Supplier can offer alternative products in case of supply difficulties
- Suppliers maintain stocks at their premises
- Monthly regular orders are made, rather than bulk orders

The way forward for a sustainable healthcare system was discussed. An area of interest which is evolving is the implementation of innovative risk-sharing agreements or managed entry agreements. CPSU has introduced the use of compassionate programmes. These patient centred strategies can improve adherence to clinical guidelines improving patient experience. With the current health expenditure and the lack of innovative treatments, it would be a moving forward step to investigate this pathway. The models being discussed include sharing cost savings with a new

introduction, pay according to positive outcome measures and stop paying if treatment fails. The main focus of the reforms is to reduce the total cost and the savings accrued are used to treat more patients and introduce new treatments. This strategy would require the setting up of patient registers to support the implementation. It is important to maintain measurable results through key performance indicators such as number of shortages, better quality of life, reduction of hospital admissions cost and reduction in re-admission costs.

Collaboration both at EU level and at national level with the regulators and HTA bodies is important to face these challenges which are being presented not only in Malta but throughout Europe. The aim is to continue to take a series of proactive measures to ensure that patients' needs are being addressed on time and in the right way. It is also important to maintain actively the engagement with all relevant stakeholders in an effort to face challenges in a combined systematic approach. Join resources and sharing expertise is essential.

APPENDIX 9

Decision of the Executive Director on a 1-year pilot initiative for fee reductions for notifications of parallel distribution in the Maltese language

17 December 2015
EMA/677790/2015
Deputy Executive Director

Decision of the Executive Director

on a 1-year pilot initiative for fee reductions for notifications of parallel distribution in the Maltese language

THE EXECUTIVE DIRECTOR

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (hereafter 'the Agency') (Founding Regulation) and in particular Article 57(1)(o) thereof,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 06 November 2001 on the Community code relating to medicinal products for human use and in particular Article 76(4) thereof,

Having regard to Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, and in particular Article 9(1) thereof,

Having regard to the Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Agency for the evaluation of medicinal products, and in particular Annex III, Number 3 thereof,

Having regard to the Financial Regulation of the European Medicines Agency and its implementing rules and in particular Article 29(1) and (2) 2nd sentence of the Financial Regulation,

Having regard to the analysis on accessibility to centrally authorised products in the Maltese language on the Maltese market, carried out by the Maltese Medicines Authority (pmjjb010/2015 of 22.09.2015 and annexes),

Having regard to currently no (zero) notices for parallel distribution being available in the Maltese language on the Maltese market,

Having regard to the consultation with the competent scientific committee (CHMP 19.11.2015) regarding the exceptional circumstances and the imperative reason of public health for parallel distributions in the Maltese language,

Whereas the Executive Director may, without prejudice to more specific provisions of Union law, in exceptional circumstances and for imperative reasons of public or animal health, grant fee reductions case by case after consultation of the competent scientific committee,

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Whereas it is imperative for the health of European citizens that language is not an obstacle to access centrally authorised medicinal products,

Whereas based on the data provided by the Maltese Medicines Authority, the level of fees charged by the European Medicines Agency for processing notifications for parallel distribution could potentially contribute to the lack of parallel distribution notifications for medicinal products in the Maltese language,

Whereas the expected impact of the pilot initiative will not lead to an increase in resources needed at the Agency,

Whereas appropriations shall be used in accordance with the principles of sound financial management whilst respecting the principle of efficiency aiming for the best relationship between resources employed and results achieved,

Whereas for the value of the fee charged for initial notifications of parallel distribution and any subsequent procedure thereof it is not deemed efficient to require case-by-case decisions on potential reduction for a predefined duration (pilot initiative).

HAS DECIDED

Article 1 - Scope and duration of the pilot initiative

Fee levels comparable to the parallel import fees charged in Malta shall be introduced for a limited period as a pilot initiative.

The duration of the pilot initiative shall be one year from 1 January 2016 to 31 December 2016.

Article 2 - Fee reductions

The applicable fee for parallel distribution shall be reduced to the comparable level as charged by the Maltese Medicines Authority for its related services for non-centrally authorised products as set out below.

Initial notification of parallel distribution	~~3 020 EURO~~ reduced to 450 EURO For each EU presentation of a medicinal product distributed in Malta in the Maltese language. [..]
Notification of changes	~~580 EURO~~ reduced to 280 EURO For each notification of changes to a notice in the Maltese language that is not submitted as part of the annual update notification and is not a safety update. [..] [..]
Notification of bulk changes	~~3 020 EURO~~ reduced to 450 EURO For one or more changes that affect all of a parallel distributor's initial notifications in the Maltese language, at any point in time after the approval of the initial notification. The scope(s) of the changes are limited to: a change in the name and/or address of a parallel distributor, addition or deletion of a re-packager, and/or a change in the name and/or address of a re-packager.

Article 3 - Exclusions

As the duration of the pilot initiative is set at one calendar year, fees for annual updates will not apply and corresponding reductions are herewith not provided for.

Article 4 - Ex-post evaluation

Within three months of the end of the pilot initiative, the Agency will collect the following data from the Maltese Medicines Authority

- An analysis on the effect that notices for parallel distribution in the Maltese language had on the number of centrally authorised products (CAPs) available on the Maltese market during the period of the pilot initiative
- An analysis on the effect that notices for parallel distribution in the Maltese language had on the availability of ATC codes of CAPs on the Maltese market during the period of the pilot initiative

The Agency shall supply the Maltese authorities with the details of all notices for parallel distribution issued in the Maltese language during the period of the pilot initiative.

Article 5 - Processing of fee reductions

During the period of the pilot initiative, any request for notifications for parallel distribution in Malta in the Maltese language, submitted to the Agency using the Agency's procedure, will be assigned the applicable reduced fee. No separate request for fee reduction by the applicant is required during this period.

Article 6 - Entry into force

This decision shall enter into force on 1 January 2016 and shall be valid until 31 December 2016.

London, 17 December 2015

Signature on file

Guido Rasi
Executive Director

APPENDIX 10

Dissemination of results

Abstract Submission

Pharmaceutical sciences

Regulatory Sciences

FIP-824

Evolvement of european union regulations on innovative medicines

Roberta Agius, Francesca Wirth[1], Anthony Serracino Inglott[*] [2]

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My preferred method of presentation is: Poster Presentation

Background: Regulatory requirements are a major reason affecting access to innovative medicines (IM).

Purpose: To study the impact of European Union (EU) regulation regarding IM by investigating authorisation procedures.

Methods: Analysis of EU regulatory tools developed to facilitate access to IM was undertaken. Conditional (CMA) and exceptional circumstances (EC) authorisations were studied using the European Public Assessment Reports as the data source. Existing legislative tools were explored to identify challenges and optimise IM access in Malta.

Results: Since 2001, 65 IM products were centrally authorised using CMA and EC procedures (35 CMA, 30 EC). Forty-three percent (n=28) were given a new active substance status and 51% (n=33) given orphan designation. In 2015, there were 822 centrally authorised products (CAPs) covering 522 Anatomical Therapeutic Chemical (ATC) Codes. The Maltese National Health Services formulary does not cover 322 (61%) CAP ATC codes. Parallel distribution (PD) was explored as a tool to increase access of CAPs. Together with the European Medicines Agency (EMA), a one-year pilot project with fee reductions for PD notifications for CAPs in the Maltese language was launched in 2016, where PD of pegfilgrastim, cetuximab, epoetin beta and amifampridine were authorised.

Conclusion: Regulatory tools such as CMA and EC authorisations are used successfully to improve access to IM, particularly in rare diseases. Targeted regulatory initiatives, as exemplified by the pilot PD project specifically authorised by the EMA for Malta, may help to overcome accessibility barriers especially in small countries.