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THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

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Actifed*

Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED**. ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg**. PHARMACEUTICAL FORM:** Oral Solution and Tablets**. INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine**. DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years**.** In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor**. CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure**. PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment**. INTERACTIONS:** Sympathomimetics; MAOI's**. ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement**. PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child**. PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets**.** Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101-7 **Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years**. For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel**.** 21238131**. Date of preparation:** January 2015

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd(Tel: +356 21238131)

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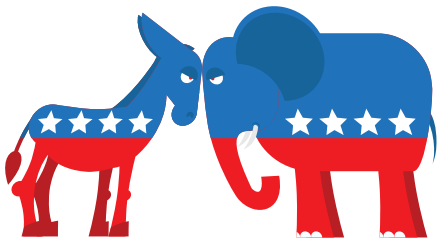
References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

US ELECTIONS 2016

OBAMACARE VS TRUMPCARE



The US Presidential election will be held on 8 November 2016. There are two contenders, the billionaire 69-year old Donald Trump [Republican] and the millionaire 68-year old Hilary Clinton [Democrat]. Trump represents a conservative party and indeed *seems* to be more conservative than Clinton in all spheres. However, conservatives are facing a Hobson's choice. The reason for this is that Trump *seems* to be the most liberal candidate in the party's history. It is been rumoured that if Trump wins the election, the Republican Party will become essentially what the Democratic Party of the 1990's was under Bill Clinton.

Representing two opposing parties, quite naturally, Clinton and Trump have divergent views on a number of key issues, one of which is the future of Obamacare. Whilst Clinton wants to improve Obamacare, Trump wants to repeal it. However, before proceeding further, it is important to illustrate the current state of affairs relating to healthcare in the US. One of the landmark reforms relating to healthcare which have been implemented in the US is the *Patient Protection and Affordable Care Act*, also known as Obamacare, which in 2010 reformed Medicare, the latter being in existence since 1966. Obamacare enacted a comprehensive system of mandated health insurance with its aim being extending health insurance coverage to those who lack it, including those people who receive no coverage from their employers, the poor and the elderly. To achieve its aims, Obamacare offers subsidies to make insurance coverage more affordable and also creates marketplaces - with websites similar to online travel sites - where individuals can compare prices as they shop for coverage. It aims to reduce the cost of insurance by enrolling younger (healthier) people into the insurance system. In addition, the law bans insurance companies from denying health coverage to people with pre-existing health conditions, allows young people to remain on their parents' plans until 26 years of age, and expands the eligibility of the public health programme for the poor. It also requires companies with more than 50 full-time employees to offer mandatory health coverage. The law aims to eventually slow the growth of US healthcare spending, which is the highest in the world (as of 2013, excluding investment, health expenditure as a share of GDP was 16.4% for the US and an average of 9% for European countries).

Returning to the future of Obamacare, contrary to Clinton's intention of strengthening and expanding Obamacare, in Trump's plan for healthcare reform, he declares that he would repeal Obamacare since he deems it unconstitutional to oblige people to have a mandatory insurance. Trump's vision also advocates [1] interstate sale of health insurance with a view to lower prices because of competition, [2] deducting health insurance premium payments from individuals' tax returns similar to what businesses do and [3] price transparency from all healthcare providers, especially medics, clinics and hospitals. In tandem, Trump vehemently opposes the provision of healthcare to irregular immigrants, which he claims cost the US an annual $11 billion. The latter provision contrasts deeply with Clinton's view since she seeks to expand access to affordable healthcare regardless of immigration status. Indeed, Clinton sponsored the Legal Immigrant Children's Health Improvement Act of 2007.

Interestingly, both Clinton and Trump want government to negotiate with pharmaceutical companies to slash prices of medicines. This intention was heralded by the price hike of an old anti-parasitic drug Daraprim® (pyrimethamine). Although Daraprim® has been off-patent since the 1970s, following the acquisition of its marketing rights by Turing Pharmaceuticals in 2015, Turing increased the price from $13.50 to $750 per tablet. This was made possible because of the drug's limited patient population, the absence of competing manufacturers, and a lack of therapeutic alternatives, effectively creating a monopoly. However, this turned the cost of prescription drugs into a political issue with health care analysts envisaging a catch 22 in the proposed governments' intervention in pharmaceutical pricing … allowing the government to exert such influence could have unintended consequences, like suppressing drug company revenues which will inevitably cut back on research.

Notwithstanding the above, we are discussing politics after all, where candidates talk the talk but often, do not walk the walk. Despite all the confrontational drama with pharmaceutical companies, this industry continues to heavily finance candidates in their electoral run … to date, donating $7 million to presidential candidates in the 2016 presidential election, according to the Centre for Responsive Politics.

Cover: Lazaretto, Manoel Island. Under the Knights of St John and during the British period, maritime travellers who arrived in Malta, especially when plague and cholera were prevalent in Europe and eastern Mediterranean coastal lands, were kept for periods in quarantine, as detailed by the health authorities and kept under observation at the Lazaretto.

Photo Credit: MIDI plc

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GMS GERMAN-MALTESE MEDICAL SOCIETY

MMSA

MPSA

MADS Malta Association of Dental Students

The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

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A maintenance bronchodilator treatment for patients with COPD who are breathless

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umeclidinium/vilanterol
breathe...

Anoro® Ellipta® (umeclidinium bromide/vilanterol) Abridged Prescribing Information

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Kindly consult the full Summary of Product Characteristics (SmPC) before prescribing

Trade Name: Anoro® Ellipta® **Active Ingredients:** 55 micrograms umeclidinium bromide and 22 micrograms vilanterol (as trifenatate). **Pharmaceutical Form:** 55 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** Maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD). **Dosage and administration:** Inhalation only. One inhalation once daily of Anoro® Ellipta® at the same time of the day. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate). **Precautions:** Anoro® Ellipta® should not be used in patients with asthma. Treatment with Anoro® Ellipta® should be discontinued immediately in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists and sympathomimetics therefore Anoro® Ellipta® should be used with caution in patients with severe cardiovascular disease. Anoro® Ellipta® should be used with caution in patients with urinary retention, narrow angle glaucoma, convulsive disorders, thyrotoxicosis, hypokalaemia, hyperglycaemia and severe hepatic impairment. No dosage adjustment is required in the elderly, in renal impairment or mild to moderate hepatic impairment. **Acute symptoms:** Anoro® Ellipta® is not indicated for acute episodes of bronchospasm. Warn patients to seek medical advice if use of short-acting inhaled bronchodilator increases. A re-evaluation of the patient and of the COPD treatment regimen should be undertaken. **Interactions with other medicinal products:** Interaction studies have only been performed in adults. Avoid beta- adrenergic blockers since this may weaken or antagonize the effect of $beta_2$-adrenergic agonists. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin). Anoro® Ellipta® should not be used in conjunction with other long-acting muscarinic antagonists, long-acting $beta_2$-adrenergic agonists or medicinal products containing either of these agents. Caution is advised with concomitant use with methylxanthine derivatives, steroids or non-potassium-sparing diuretics as it may potentiate possible hypokalaemic effect of $beta_2$-adrenergic agonists. **Fertility, pregnancy, and breast-feeding:** No available data. Balance risks against benefits. **Side effects:** Common: Urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth. Uncommon: Atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash. **Legal category:** POM. **Presentation:** Anoro® Ellipta®. 1 inhaler x 30 doses. Anoro® Ellipta® 55/22mcg. **Marketing authorisation (MA) nos:** 55/22mcg 1x30 doses [EU/1/14/898/002]; **MA holder:** Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK. **Last date of revision:** October 2014. Anoro® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. Anoro® Ellipta® was developed in collaboration with Theravance, Inc.

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***Gibraltar:* alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA):** https://yellowcard.mhra.gov.uk/

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

MLT_GIB/UCV/0004/15 Date of preparation: March 2014

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Dr Mark Xuereb MD (Melit.) MRCPsych(UK) MRCEM(UK) MMCFD (Melit.) is a UK-trained crisis psychiatrist. He was a clinical supervisor at Downing College, Cambridge University and lecturers locally in the Departments of Psychiatry and Gerontology. He presently leads crisis teams, being based at Mater Dei Hospital.

ISSUE GUIDE

TheSynapse

The Powerful Amoxicillin + Clavulanic Acid Combination

Forcid Solutab®:

- Contains amoxicillin and clavulanic acid in the ratio 7:1, the powerful combination to fight infections in unique Solutab® formulation

Forcid Solutab® indications:

- Acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia.
- Cystitis, pyelonephritis.
- Skin and soft tissue infections in particular cellulitis, animal bites.
- Severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Forcid Solutab® offers a convenient antibiotic therapy for adults and children:

- Easy and flexible administration, the unique versatile formulation can be swallowed intact or dissolved in water.
- Equally effective whether dissolved in water or taken as a tablet and rapidly absorbed.[1]
- Suitable for a wide range of patients: no sugar, no gluten, no sodium, no lactose.

Forcid Solutab® dosing in adults and children ≥ 40 kg:

- Standard dose of Forcid Solutab 1000 is 2 times a day.
- For infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections, Forcid Solutab1000 is recommended to be given 3 times per day.

Forcid® 1000 Abbreviated Prescribing Information. Presentation: Forcid® 1000, containing as active substances amoxicillin and clavulanic acid. Each tablet/dispersible tablet contains 875 mg amoxicillin as amoxicillin trihydrate and 125 mg clavulanic acid as potassium clavulanate. **Indications:** Amoxicillin/clavulanic acid tablets are indicated for the treatment of the following infections in adults and children: acute bacterial sinusitis (adequately diagnosed), acute otitis media, acute exacerbations of chronic bronchitis (adequately diagnosed), community acquired pneumonia, cystitis, pyelonephritis, skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis, bone and joint infections, in particular osteomyelitis. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Duration of therapy:** The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review. **Posology:** The dose of amoxicillin/clavulanic acid that is selected to treat an individual infection should take into account the expected pathogens and their likely susceptibility to antibacterial agents, the severity and site of infection, the age, weight and renal function of the patient. **Adults and children over 40 kg:** The standard dose of Forcid 1000 is 2 times a day. For infections such as otitis media, sinusitis, lower respiratory infections and urinary tract infections, Forcid 1000 is recommended to be given 3 times per day. **Children under 40 kg:** 25mg/3.6mg/kg/day to 45mg/6.4mg/kg/day given as 2 divided doses. No clinical data are available for amoxicillin/clavulanic acid 7:1 formulations higher than 45mg/6.4mg/kg per day in children under 2 years. There are no clinical data for amoxicillin/clavulanic acid 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population cannot be made. **Elderly patients:** No dose adjustment is necessary. **Patients with impaired renal function:** No dose adjustment in dose required in patients with creatinine clearance (CrCl) greater than 30ml/min. In patients with CrCl less than 30ml/min, use of Forcid 1000 is not recommended as no recommendations for dose adjustments are available. **Patients with impaired liver function:** Dose with caution and monitor hepatic function at regular intervals. **Method of administration:** Amoxicillin/clavulanic acid tablets are for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption. Forcid tablets can be swallowed whole with a glass of water, or first dissolved in a ½ cup of water (at least 30ml) and stirred thoroughly before swallowing. **Contraindications:** Hypersensitivity to the active substances, to any penicillins or to any of the excipients. History of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **Special warnings and precautions for use:** Before initiating therapy, careful enquiry should be made of previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in patients with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid must be discontinued and appropriate alternative therapy instituted. If an infection is proven to be due to amoxicillin-susceptible organism(s), consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance. This presentation of amoxicillin/clavulanic acid is not suitable for use when there is high risk that presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should also not be used to treat penicillin-resistant *S. pneumonia*. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Avoid if infectious mononucleosis is suspected. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. Prolonged use may result in overgrowth of non-susceptible organisms. Occurrence of feverish generalised erythema associated with pustula at treatment initiation may be a symptom of acute generalised exanthemous pustulosis (AGEP) and requires treatment discontinuation and contra-indicates any subsequent administration of amoxicillin. Use with caution in patients with evidence of hepatic impairment. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects. Antibiotic-associated colitis has been reported, consider in patients who present with diarrhoea. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation. Periodic assessment of organ system functions is advisable during prolonged therapy. Prolongation of prothrombin time was reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. In patients with renal impairment, dose should be adjusted according to degree of impairment. In patients with reduced urine output, crystalluria has been observed very rarely, mainly with parenteral therapy. Maintain adequate fluid intake and urinary output during administration of high doses of amoxicillin to reduce possibility of amoxicillin crystalluria. If bladder catheter is in-situ, check patency. False positive results may occur when testing presence of glucose in urine with non-enzymatic methods during treatment of amoxicillin; use enzymatic glucose oxidase methods. Clavulanic acid in Forcid may cause non-specific binding of IgG and albumin by red cell membranes leading to false positive Coombs test. Reports of positive test results using Bio-Rad Laboratories Platelia *Aspergillus* EIA test; cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported; positive results should be interpreted cautiously and confirmed by other diagnostic methods. Forcid 1000 contains 0.64 mmol potassium per tablet (25 mg). **Pregnancy and lactation:** Use in pregnancy should be avoided unless considered essential by physician. Both amoxicillin and clavulanic acid are excreted in breast milk; consequently diarrhoea and fungus infection of mucous membranes is possible in breast-fed infants. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by physician in charge. **Undesirable effects:** The most commonly reported adverse reactions (ADRs) are diarrhoea, nausea and vomiting. For a full listing of undesirable effects, refer to the complete Summary of Product Characteristics for Forcid 1000. Marketing authorization holder: Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. 13-FOR-003 Adverse events should be reported to the local regulatory authority and Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. Please read carefully the instructions on the package leaflet. 13-FOR-004 102013

Reference: 1. H. Sourgens et al. International Journalof Clinical Pharmacology and Therapeutics. 2004; 42: 165-173.

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THE DARK MATTER OF THE GENOME

SOME INSIGHTS AND CLINICAL APPLICATIONS

ALFRED GRECH & MICHAEL BALZAN

ABSTRACT

Only approximately 1.5% of the human genome encodes protein sequence; the rest is 'dark matter'. Research on these noncoding regions shows that they play roles in cellular homeostasis, development, differentiation and metabolism. Cancer, cardiovascular, developmental, and neurological diseases are characterised by aberrant expression of these regions. Exploring their clinical utility as biomarkers and molecular targets in medical theranostics is a very promising way forward.

INTRODUCTION

It is now well known that only approximately 1.5% of the human genome encodes protein sequence.[1] However, comparative analyses with mammalian genomes have shown that at least 5% is under selective constraint and thus probably functional, of which approximately 3.5% consists of noncoding elements with apparent regulatory roles.[2] Collectively, this created an aura of mystery, leading to the label of 'dark matter', in a manner analogous to the 'dark matter' of the universe, which we can neither easily detect nor understand, but that nonetheless exists and is open to experimental queries. Ongoing research on these noncoding regions, which form a major part of this once proverbial genomic 'dark matter', shows that they play vital biological roles in cellular homeostasis, development, differentiation and metabolism. Indeed, their aberrant expression is being found in a variety of human diseases, including cancer, cardiovascular, developmental, and neurological diseases. Consequently, translational research is exploring the clinical utility of these noncoding RNAs (ncRNAs) as biomarkers and molecular targets in medical theranostics.

THE DARK MATTER IN THE CLINIC

ncRNAs represent a significant portion of the human transcriptome. Based on their size, ncRNAs are grouped into two major classes, namely, small ncRNA and long ncRNA (lncRNA). microRNAs (miRNAs, approximately 22 nucleotides long) and transcription initiation RNAs (tiRNAs, 18 nucleotides long) are two examples of the first class. In contrast, lncRNAs, which resemble mRNA transcripts, range from 200 nucleotides to approximately 100 kilobases.[3] In humans, lncRNAs have been identified to be transcribed from four chromosomal regions, termed the *Hox* gene loci. These four *Hox* loci (*Hoxa*, *Hoxb*, *Hoxc* and *Hoxd*) include dozens of genes that are involved in a variety of biological processes, including embryonic development, cell differentiation and tumorigenesis.[4]

Several lncRNAs are coded from regions between the genes in these *Hox* clusters, hence their other name being long intergenic non-coding RNA, or lincRNA. Increasing numbers of lncRNAs are being identified and their functions investigated. In fact, an emerging function is their role in genome modification, where they associate with Polycomb proteins to epigenetically silence genes. Specifically, this can occur through histone tail post-translational modifications, with methylation of histone H3 lysine 9 (H3K9me), lysine 27 (H3K27me), and histone H4 lysine 20 (H4K20me) being associated with regions of the genome that are transcriptionally inactive. Such silencing of genes through histone methylation is thought to be mediated by chromatin modelling complexes such as the Polycomb repressive complexes (PRC), PRC1 and PRC2. In this review, we will focus on what are perhaps the three most valued Polycomb-related lncRNAs in the clinical setting, i.e. ANRIL, HOTAIR, and XIST.

1. ANRIL

Spanning 126.3 kilobases in the genome, ANRIL is an antisense ncRNA in the INK4 locus. The INK4b (p15)–ARF (p14)–INK4a (p16) locus, which is found on chromosome 9p21, is said to be an essential regulator of cellular senescence. INK4 carries out this regulatory role by coding for three tumour suppressors i.e. p14 which increases p53 signalling, and p15 and p16, which (a) promote the function of the retinoblastoma protein pRB, and also, (b) inhibit cyclin-dependent kinases therefore causing cell cycle arrest. Regulation of the INK4 locus is governed by the Polycomb repressive complexes PRC1 and PRC2, where PRC2 initially trimethylates H3K27 in the transcriptionally silent heterochromatin, and then PCR1 recognises the methylated H3K27 as a sign to maintain the heterochromatin. Both *cis*- and *trans*-acting lncRNAs recruit Polycomb complexes to establish the heterochromatin. In this case, PRC1 and PRC2 are recruited to the INK4 locus by the lncRNA ANRIL, which is expressed antisense to the p14 and the p15 tumour suppressors.

It has been suggested that both Polycomb repressive complexes are recruited in *cis* to the INK4 locus gene through association with nascent ANRIL transcripts. Such a suggestion was made following results from a study showing that ANRIL knockdown leads to the upregulation of p15 and p16. Furthermore, the transcriptional state of the locus, which is often deleted or silenced in cancer, appears to be affected by changes in ANRIL expression.[5] Upregulation of ANRIL is seen in prostate cancer tissues for instance,[6] and in heart disease, type 2 diabetes, and risk-associated single-nucleotide polymorphisms (SNPs) for cancers overlapping with the ANRIL region.[7] One SNP in the 9p21 gene desert was also shown to be associated with coronary artery disease; this DNA variant disrupts the binding site for the STAT1 transcription factor which is known to represses the expression of ANRIL. Therefore, by stopping STAT1 from binding, it leads to the upregulation of ANRIL, and the cause behind coronary artery disease might well be the ANRIL-mediated silencing of p15.[8] Similar to ANRIL is the lncRNA HEIH which was also found to regulate the INK4 locus, where by recruiting PRC2 to tumour suppressors, it facilitates hepatocellular carcinoma tumorigenesis.[9]

2. HOTAIR

HOTAIR is one of the recently identified lncRNAs. It is a 2,158-nucleotide-long, spliced and polyadenylated lncRNA, encoded by a 6,232 base pair gene, located in the *Hoxc* cluster on chromosome 12 (specifically at 12q13). Only one strand of HOTAIR, which is antisense to the canonical *Hoxc* genes, is transcribed; hence its name, standing for *Hox* Antisense Intergenic RNA.[10] Unlike other documented lncRNAs that act strictly in *cis* (such as XIST), HOTAIR is the first lncRNA that is said to function in *trans*, because it is transcribed by one chromosome (chromosome 12), but regulates chromatin domains on another chromosome.[11] HOTAIR exists only in mammals, has been highly conserved in primates throughout evolution, and has evolved faster than nearby *HoxC* genes. Poorly conserved sequences are present in its six exons, except for a 239 base pair domain in exon 6, which is particularly conserved.[12]

Presently, the proposed functional mechanism of HOTAIR is to act as a scaffold for the recruitment and binding of the polycomb complex PRC2 and lysine-specific demethylase 1 (LSD1). PRC2 and LSD1 are multisubunit protein complexes that epigenetically modify chromatin. HOTAIR is believed to recruit these two complexes to regions of the genome so as to bring about gene silencing. For this reason, HOTAIR is emerging as an important player in tumorigenesis. It was found that high levels of HOTAIR are linked with metastatic spread and poor survival rate in breast cancer.[13] Specifically, HOTAIR was shown to be highly upregulated in primary and metastatic breast tumours, even up to two-thousandfold over normal breast tissue. HOTAIR expression levels were also found to correlate with metastasis in colorectal cancer,[14] gastrointestinal stromal tumours,[15] hepatocellular carcinoma,[16-17] and pancreatic cancer.[18]

THE MAIN CHALLENGE IN INTRODUCING ncRNA-BASED THERAPEUTICS INTO CLINICAL PRACTICE IS THE DELIVERY AND THE OFF-TARGET EFFECTS

3. XIST

XIST, or X inactive specific transcript, is a mammalian lncRNA located in the X chromosome inactivation centre. Its gene product is first transcribed from the inactive X chromosome, and then, it spreads along the same X chromosome from which it was transcribed. In mammals, silencing of one of the two X chromosomes is necessary to achieve dosage compensation. The lncRNA XIST triggers X chromosome inactivation (XCI) in cells of the early embryo and in hematopoietic progenitors where silencing factors are present. XIST is not however required for the maintenance of XCI. XIST is also found to be expressed in adult females, and for this reason, it is suggested that the loss of XIST in adults could lead to the reactivation of inactive X genes. Having said this, the exact molecular mechanism by which XIST inactivates the X chromosomes remains unclear.

Nonetheless, surmounting evidence suggests that XIST has a role in the differentiation and proliferation of human cells. In fact, the dysregulated expression of XIST may play a pathologic role in cancer, which could be related to changes in gene expression, from the alterations to the stability of heterochromatin. It is possible that cancer cells produce silencing factors that allow for the inactivation of the X chromosome outside of the context of embryonic development. SATB1 (or special AT-rich sequence-binding protein-1), for instance, has been identified as a factor related to XIST-mediated chromosome silencing, and its aberrant expression was shown to promote breast, hepatocellular, prostate and other types of cancer.[19] XIST silencing has also been reported in transgenic male fibrosarcoma cell lines, again suggesting a special context whereby X chromosome inactivation through XIST can occur in cancer cells.[20]

CONCLUSION

ANRIL, HOTAIR and XIST are merely three of the ncRNAs that are currently being investigated. To mention but a few, others include Dleu2, EGO, lncRNA-a7, lncRNA-P21, and MEG3, each with an equal potential for being the missing piece of the puzzle. It is not therefore impossible to envisage a therapeutic world based on ncRNAs. Presently, however, the main challenge in introducing ncRNA-based therapeutics into clinical practice is the delivery and the off-target effects. Breakthroughs in both of these areas will pave the way forward for the future of medicine.

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Amoxicillin/Clavulanate Potassium

Powder for oral suspension

- ✓ Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- ✓ Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- ✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

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Mini Abridged Prescribing Information: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATION:** 600 mg/42.9 mg/5 ml powder for oral suspension. Supplied in 100 ml glass bottle with a dosing spoon. **INDICATION:** treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose is 90/6.4 mg/kg/day in two divided doses. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to SPC's for full list of undesirable effects*. **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2014. **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).** ***REPORTING ADVERSE EVENTS (AEs):*** **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). **Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

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'SURGICAL PATHOLOGY' – WHAT'S IN A NAME?

Editor's note: The Synapse is pleased to introduce a new series consisting of 'Medical Anecdotes' … short accounts of interesting cases, some medical disasters, involving pathology and clinical practice, from the recollection of **Prof. Albert Cilia-Vincenti.**

The American name for 'histopathology' (also known as 'cellular', 'tissue' or 'anatomic' pathology) is 'surgical pathology', and there is medical history behind this label. In the 19th century, big American surgical departments were increasingly dissatisfied with reports from pathology colleagues. Surgeons were mainly interested in prognosis after excision of a diseased tissue or organ, and not in detailed microscopic descriptions devoid of any clinically useful information. They eventually decided that the pathological examination of their surgical specimens would be carried out in-house. This is why, in some of the larger American institutions, the surgical pathology department, including the frozen section room, is located within the surgical department.

These 'novel concept' surgical pathology departments immediately set about researching morphological clues to prognosis which, in the main, consisted of painstaking patient follow-up and histology review. One important breakthrough of this research was the identification of a group of pseudo-sarcomatous lesions. These mimicked sarcoma both clinically and microscopically. However, these pseudo-sarcomatous lesions had been responsible for many unnecessary limb amputations.

In the mid-1960s a Maltese medical student was suffering from a recurrent tumour in his right leg's peroneal compartment muscles, which was diagnosed as fibrosarcoma. He struck it lucky when his Maltese surgeon declined to perform the indicated amputation himself and referred him to London's Royal Marsden Hospital (previously called The Royal Cancer Hospital).

His luck consisted in that the pathologist at the Royal Marsden had just seen a paper by Arthur Purdy Stout, an American surgical pathologist, describing a number of pseudo-sarcomas, including a so-called "desmoid" tumour (now classified as 'infiltrative fibromatosis'), and how to distinguish them microscopically from sarcoma. The paper detailed how these lesions were locally infiltrative like sarcoma but did not metastasize. Most of them occurred in the anterior abdominal wall muscles in women, apparently after pregnancy, and in limb muscles in both sexes, predominantly in the young, with a high recurrence rate after attempts at local excision, and a tendency not to recur further after increasing age.

The Maltese student had first noticed his leg tumour in his late teens and in total, had undergone four attempts at excising it, twice in Malta and twice in London. The latter two operations involved block dissections of lateral calf muscles, including excision of the fibula with the whole peroneal compartment muscles in the first of these operations. Recurrence did not occur after the fourth operation when he reached age 25. Many other young people have been spared limb amputations by the clinical research of American surgical pathologists.

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Prolonged release tablets

- ✓ Unique bilayer tablet with immediate and sustained release delivery of amoxicillin provides superior efficacy against resistant pathogens[1,2]
- ✓ Recommended by leading Guidelines in the treatment of Community Acquired Pneumonia[3,4]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis[5]
- ✓ Indicated for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days[5]

Spreading infectious liveliness!

Mini Abridged Prescribing Information: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** Augmentin SR. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATION:** 1000 mg/62.5 mg prolonged-release tablets. Supplied in 28 tablet packs. **INDICATION**: Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose of two tablets twice daily for seven to ten days. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains 29.3 mg (1.3 mmol) of sodium per tablet. *Refer to SPC's for full list of precautions.* **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to SPC's for full list of undesirable effects*. **AUTHORISATION NUMBER:** AA 1051/00102. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2014. **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).** ***REPORTING ADVERSE EVENTS (AEs)*: If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). **Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

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THE EVOLUTION OF LIFE EXPECTANCY IN MALTA OVER HALF A DECADE

KATHLEEN ENGLAND, TOBIAS VOGT AND NATASHA AZZOPARDI MUSCAT

ABSTRACT

An overview of life expectancy in Malta over the past sixty years shows a remarkable increase for both men and women. However, gains in life expectancy were not constant throughout the period. The rate of increase as well as the attributable causes of the noted increase varied over the years. Disparities in life expectancy by gender and by level of education exist. Life expectancy in Malta has caught up with Western Europe over the past 30 years and now compares well with the average for the EU-15. (*The EU-15 consists of the 15 EU member states who became members in the European Union before 2004 and on average have the best life expectancies in the EU).*

INTRODUCTION

The extension of the human lifespan has been significant in recent years, with world average life expectancy at birth having more than doubled over the past two centuries[1] and rising by more than one-third in just the last four decades.[2] Life expectancy is often used by countries as a measure of population health. It is an indicator that summarizes the mortality conditions in a country in a given year. Life expectancy at birth shows the number of years that a person can expect to live if current mortality conditions would prevail in the future.

The world average life expectancy for males stood at 69 years for males and 73 years for females in 2015[3] with highest average

Relvar Ellipta is for symptomatic treatment of patients with a FEV1 <70% predicted normal (post-bronchodilator) and an exacerbation history[1]

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For many patients like Joe with a history of exacerbations, COPD already takes up too much space in their life, yet they fear losing even more. So, when they need maintenance therapy, choose new Relvar Ellipta:

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(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** *The 92 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. *The 184 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting $beta_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. *For COPD:* One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** *Hypersensitivity* to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** ***Pregnancy:*** No adequate data available. ***Lactation:*** insufficient information available. ***Fertility:*** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 *micrograms/22 micrograms inhalation powder, pre-dispensed*. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom **Marketing Authorisation Numbers:** EU/1/13/886/001-6 **DATE OF PREPARATION:** December 2013

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Gibraltar: **alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA):** https://yellowcard.mhra.gov.uk/

*Patients' current or previous maintenance inhalers: HandiHaler/ DISKUS/ MDI/ HFA (COPD); DISKUS/ MDI/ HFA (asthma).[4]

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MLT_GIB/RESP/0004/16 Date of preparation: Feb 2016

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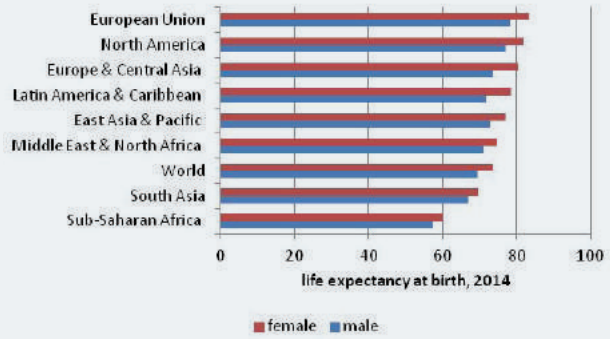

Figure 1. Life expectancy at birth in 2014 by Broad World Regions.[4]

life expectancies by broad regions being attained in Europe and North America (Figure 1).[4] In sharp contrast, life expectancy gains have been modest in Africa. In fact, due to the impact of AIDS, during the 1990s life expectancy actually decreased; however, since 2005 mortality due to HIV/AIDS has been decreasing, allowing life expectancy at birth to increase again.[5]

The original "epidemiological transition" theory by Abdel Omran[6] was the first attempt to explain the progress in healthcare made by industrialised countries over the past two centuries. Further refinements of the original theory were made and are described as the stages of the 'health transition'.[7] Between the turn of the 18th century and the 1960s, life expectancy improved dramatically from low levels of 30-35 years to reach about 70 years in the mid-1960s. This was primarily due to the reduction in mortality from infectious diseases. Improvements in living conditions, wealth and nutrition together with important public health measures including investment in safe drinking water and sewage systems were important measures responsible for major reductions in mortality from infectious diseases. This was followed by the introduction of immunisation and antibiotics. Since the 1970's, we are experiencing a second stage in health transition relating to the reduction of cardio-vascular disease, at least in high-income countries. More recently, some countries are now experiencing a third stage (possibly without having completed the previous one), which is the fight against ageing. However, these stages may occur at different times in different countries.[7]

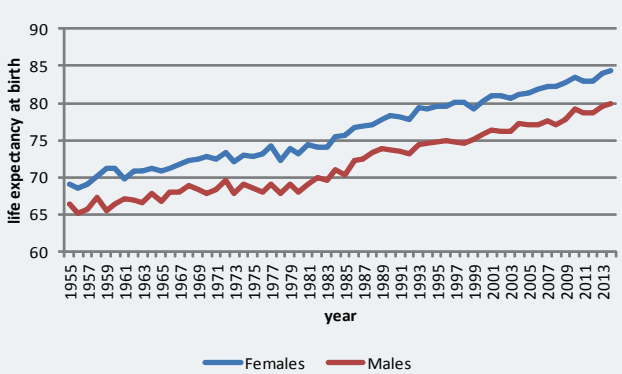

Figure 2. Trends in life expectancy in males and females in Malta

IN MALTA ... IT IS OF NOTE THAT THE GENDER GAP OBSERVED WITH LIFE EXPECTANCY DISAPPEARS WHEN CONSIDERING *HEALTHY* LIFE EXPECTANCY, INDICATING THAT THE ADDITIONAL LIFE EXPECTANCY IN FEMALES TEND TO BE LIVED WITH DECREASED HEALTH AND WITH ACTIVITY LIMITATIONS

THE SITUATION IN MALTA

An overview of life expectancy in Malta over the past 60 years has shown a steady increase (Figure 2), with life expectancy in 2014 reaching 79.97 for men and 84.37 for women.[8] However, it is well known that substantial disparities in average life expectancy exist and these are associated with socio-economic variables. Persons who have higher levels of education have a higher life expectancy at birth compared to those with lower education levels. This gap is wider for men than women i.e. Males: least educated 77.30, most educated 81.80; Females: least educated 82.40, most educated 84.10, in 2011.[9]

Over the past 60 years, gains in life expectancy varied from one decade to another. Detailed demographic analysis of gains between 1955 and 1980 reveal that the gains are attributable mainly to a fall in infant mortality, as seen in figure 3. During this period, life expectancy in the older age groups actually deteriorated resulting in an overall picture of life expectancy stagnation in the 1970s. The largest gains in life expectancy were experienced during the 1980s with more modest gains being made in the 1990s. These gains are mainly observed in the older age groups and are largely attributed to the start of a downward trend in circulatory mortality (Figure 4).

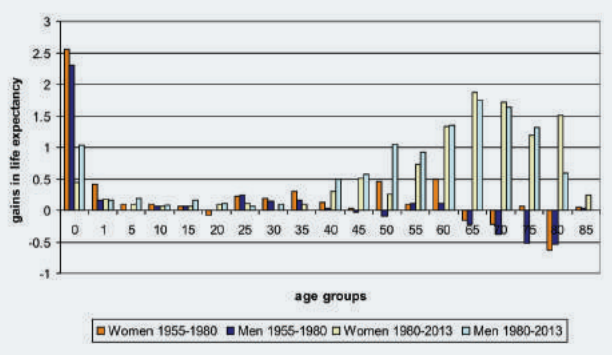

Figure 3. Gains in life expectancy in Malta by period, age and gender

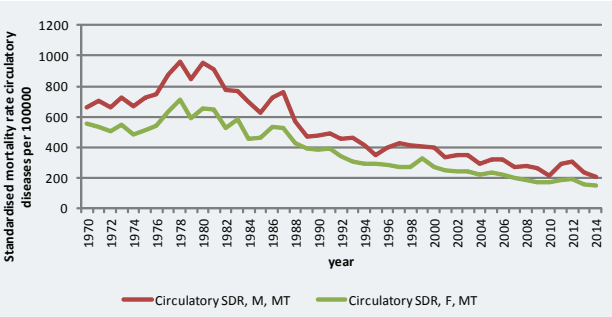

Figure 4. Trends in standardised mortality rate from circulatory diseases in Malta in males and females.[8] SDR: Standardised Death Rate, M: Male, F: Female, MT: Malta.

HOW DOES MALTA'S LIFE EXPECTANCY TRAJECTORY COMPARE TO THE EU-15?

According to the data for 2014, the life expectancy for men (79.97) and women (84.37) in Malta compares well with that of EU-15 (life expectancy for EU-15 stood at 79.06 for males and 84.23 for females); however, this has not always been the case. Figure 5 shows how life expectancy for women in Malta has been persistently lower than that of EU-15 and only seems to catch up now. In men life expectancy improvement lagged behind in the 1970s but caught up in the latter half of the 1980s and has largely remained similar to the EU-15 since then.

A gender gap of around 4.5 years in life expectancy exists between men and women in Malta. This gap has remained relatively stable over the past 40 years. The gender gap in life expectancy varies substantially between different EU-28 member states with large differences between the sexes found in Lithuania (11.1 years in 2013), and smaller differences found in the Netherlands, United Kingdom and Sweden (3.7, 3.7 and 3.6 respectively).[10]

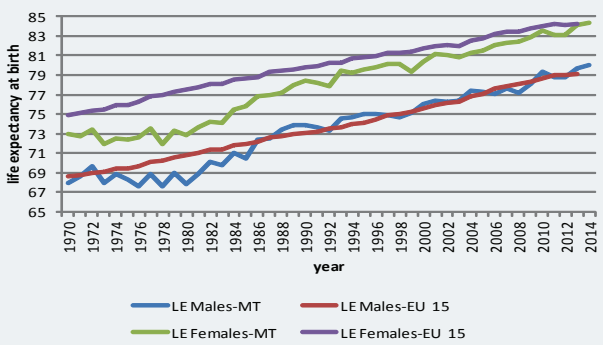

Figure 5. Trends in life expectancy at birth in males and females in Malta compared to EU 15.[9] LE: Life expectancy.

EXTREME LONGEVITY FOR MORE PEOPLE

The current data for Malta shows that the oldest recorded female death occurred at 109 years and the oldest male death occurred at 106 years. In the 1950s, deaths in the 85 plus age group accounted for 5% in men and 8% in women. In 2014 they accounted for 23% and 43% of all deaths respectively.[11] Moreover, the old age dependency ratio (represents the number of people aged 65 years and over per workers aged 15-64 years) increased from 12% and 13% in males and females respectively in 1955 to 23% and 31% in 2014. Whether extra years of life gained through increased longevity are spent in good or bad health is a crucial question. In this context indicators of health such as healthy life expectancy (HLE) are of increasing interest. HLE is defined as the number of years that a person is expected to continue to live in a healthy condition (in absence of diseases or disabilities). In 2013, the HLE at age 65 was estimated at 12.7 years for females and 12.8 for males in Malta, well above the EU-28 average (8.6, 8.5 respectively).[12] It is of note that the gender gap observed with life expectancy disappears when considering HLE, indicating that the additional life expectancy in females tend to be lived with decreased health and with activity limitations.

DISCUSSION AND CONCLUSIONS

This article has described the evolution of life expectancy in Malta over the past sixty years. It has highlighted the gender differences as well as the periods that have contributed greatest to the gains to life expectancy.

Contributions to gains in life expectancy reach far beyond the health sphere alone. While recent advances in life expectancy, at least in high-income countries, were largely due to declines in mortality from circulatory disease, this appears to be dependent on their economic growth. Transmission of knowledge and technology for the control of circulatory diseases from higher to lower income countries in Europe does not suffice and the answer may lie in developing stronger and more equitable economic conditions.[13]

Gains in life expectancy in high income countries are resulting in an increase in the old age dependency ratio. In these countries 'expected lifetime labour force participation as a percentage of life expectancy is declining'.[14] As studies suggest that life expectancy will continue to increase in the years to come,[15,16] countries facing such increase in longevity need to develop policies which will allow sustainable public pension and health care plans.

Notwithstanding this, not all countries have the same aging pattern, and migration of workers from younger, often poorer countries, to older, often richer countries, may serve to balance the global distribution of labour and capital.[2]

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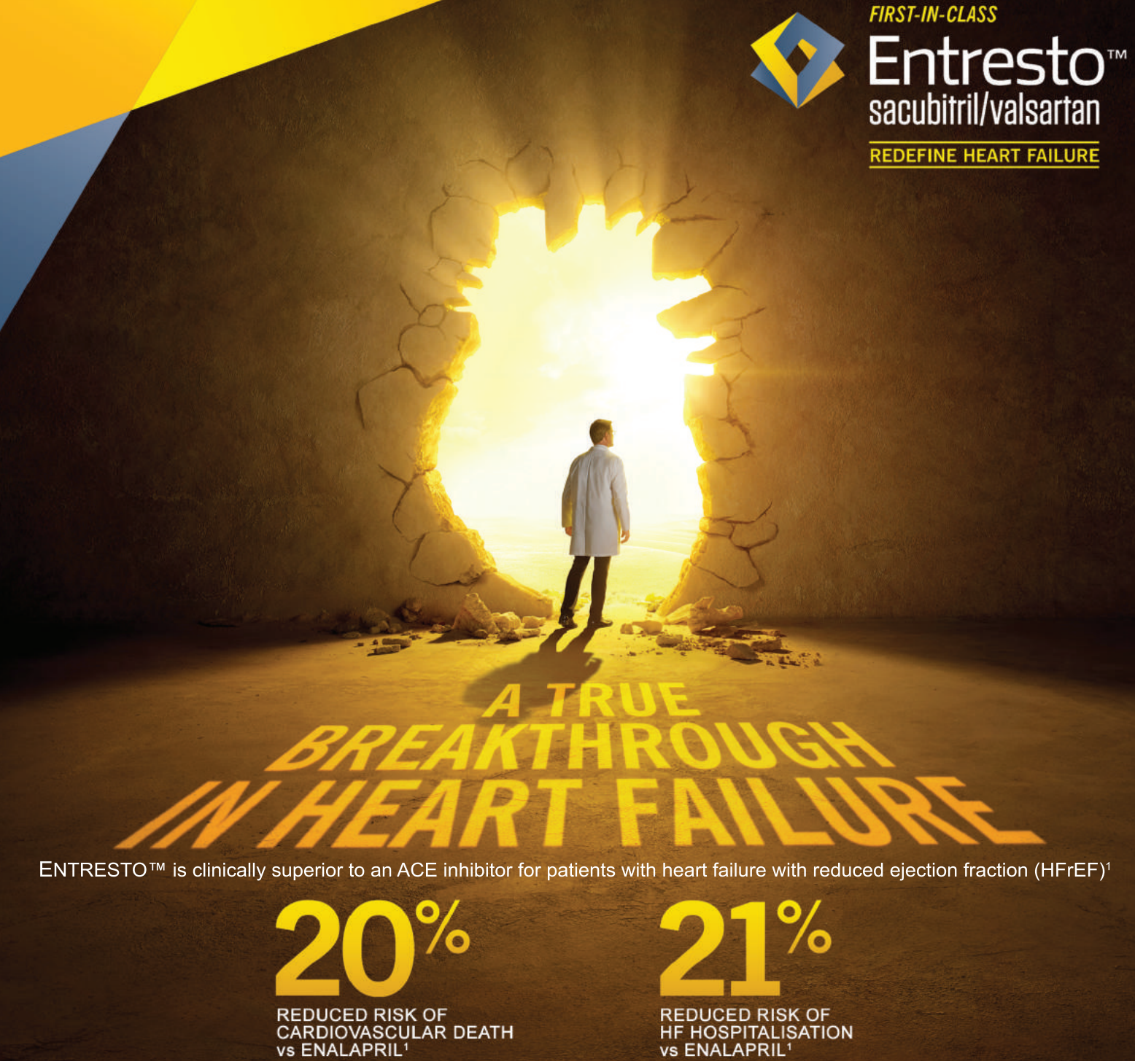


ENTRESTO™ is clinically superior to an ACE inhibitor for patients with heart failure with reduced ejection fraction (HFrEF)[1]

20%
REDUCED RISK OF CARDIOVASCULAR DEATH vs ENALAPRIL[1]

21%
REDUCED RISK OF HF HOSPITALISATION vs ENALAPRIL[1]

ENTRESTO™ ▼(sacubitril/valsartan)
Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).**Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration:** The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended din patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. **Interactions:** Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. **Fertility, pregnancy and lactation:** The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. **Undesirable effects:** Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1 000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes:** Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Frimley Business Park, Camberley, GU167SR, United Kingdom. **Marketing Authorisation Numbers:** Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. **Please refer to the Summary of Product Characteristics (SmPC) before prescribing.** Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2015-MT-ENT-19-NOV-2015

NOVARTIS PHARMACEUTICALS

ACE = angiotensin-converting enzyme

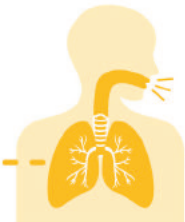
Reference: 1. McMurray JJV, Packer M, Desai AS, et al; for PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

ENT Ad1 06/16 MT

FLAME

BACKGROUND

Exacerbations
sudden worsening of COPD symptoms[1]



Prevention
a key goal of long-term COPD care[1,2]

ABOUT FLAME[3]

Head-to-head study

Ultibro® Breezhaler®*
dual bronchodilator (LABA/LAMA)

VS

Seretide®**
bronchodilator and inhaled corticosteroid combination (LABA/ICS)

*indacaterol/glycopyrronium bromide 110/50 mcg **salmeterol/fluticasone 50/500 mcg

investigating the rate of **COPD exacerbations**

in people with an history of ≥1 exacerbation in the previous year

KEY RESULTS VS SERETIDE[3]

Ultibro Breezhaler

met **primary endpoint** (non-inferiority)

showed **consistent superiority**

- **across exacerbation outcomes**

regardless of:

- **disease severity**
- **eosinophil levels** (a type of white blood cells)

moderate or severe exacerbations

17% risk reduction

prolonged time to 1st episode with a **22%** risk reduction

similar **safety profiles**

fewer cases of **pneumonia**

CONCLUSIONS[3]

Ultibro Breezhaler ▪ **more effective** ▪ than the current standard of care in reducing COPD exacerbations

These results are anticipated to impact the future care of people living with COPD

NOVARTIS PHARMACEUTICALS

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3. Wedzicha JA, Banerji D, Chapman KR. Indacaterol/Glycopyrronium Versus Salmeterol/Fluticasone for COPD Exacerbations. *New England Journal of Medicine*. 2016. Available at: www.nejm.org/doi/full/10.1056/NEJMoa1516385. Last accessed May 2016.

The First Once-Daily Dual Bronchodilator[4]

THE FIRST ONCE-DAILY DUAL BRONCHODILATOR
ULTIBRO® BREEZHALER®

Once-daily ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).[4]

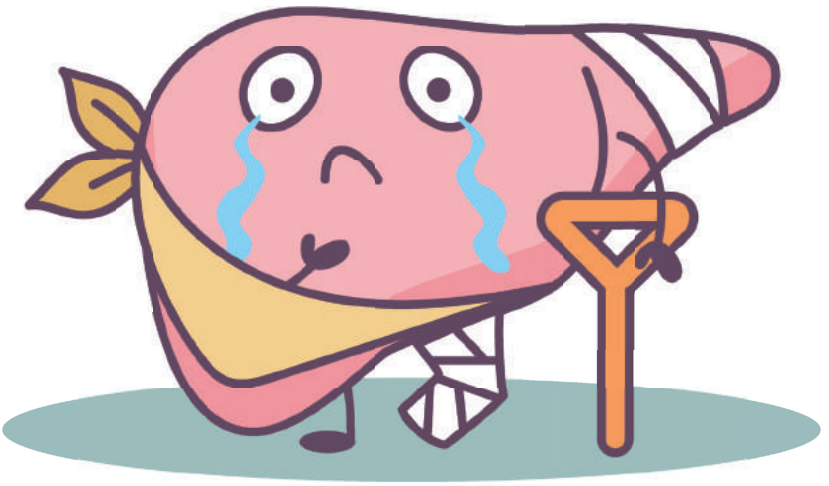
Ultibro Breezhaler inhalation powder, hard capsules

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **PRESENTATION:** Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. Method of administration For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. Asthma: Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. Urinary retention: No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 , EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872 2015-MT-ULT-09-OCT-2015

ONCE DAILY
ultibro®
breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

4. Novartis Europharm Ltd. Ultibro Breezhaler Summary of Product Characteristics.

MANAGEMENT OF ACUTE LIVER FAILURE IN ADULTS



GODFREY AZZOPARDI

ABSTRACT

Acute Liver Failure is a medical emergency characterised by cerebral oedema and non-convulsive seizures. Patients with fulminant hepatic failure need urgent workup for liver transplantation. In the meantime, a multimodal approach must be adopted to decrease the incidence of death from neurological complications.

INTRODUCTION

Acute liver failure is a rare, life-threatening condition. Often it occurs in young, previously healthy individuals. Management of these patients is extremely challenging. In view of the fact that experience in management outside specialised centres is limited, consideration for transfer to a tertiary centre with a facility for liver transplantation should be taken as early as possible. Management guidelines facilitate the standardisation of critical care management of these patients amongst different specialities, thereby promoting a smoother and more efficient continuity of care.

CLASSIFICATION OF ACUTE LIVER FAILURE

Liver failure is a triad of jaundice, coagulopathy and encephalopathy.

The O'Grady System classifies acute liver failure as:

1. Hyperacute: encephalopathy occurs within 7 days of the onset of jaundice;
2. Acute: encephalopathy occurs within 8 to 28 days of the onset of jaundice;
3. Subacute: encephalopathy occurs between 29 days to 12 weeks of the onset of jaundice.

PRESENTATION

Acute liver failure presents with acute, severe hepatitis, followed by coagulopathy (high INR) and encephalopathy. These patients typically lack the clinical and radiological signs associated with chronic liver disease, namely hepatomegaly, ascites, clubbing, leukonychia, caput medusa, spider naevi, gynaecomastia and cirrhosis. Paracetamol overdose is the commonest cause of fulminant hepatic failure in developed countries, whereas viral hepatitis is the commonest cause worldwide. The development of cerebral edema is the main cause of morbidity and mortality in patients with acute liver failure.

PATHOPHYSIOLOGY OF CEREBRAL OEDEMA IN ACUTE LIVER FAILURE

1. HYPERAMMONAEMIA

Ammonia, a normal by-product of protein metabolism, is detoxified by the liver to urea. In liver failure, failure of hepatic ammonia metabolism leads to hyperammonaemia. In the brain, ammonia is converted to glutamine. In acute liver failure, this acute rise in intra-cerebral glutamine increases the osmotic pressure in astrocytes, leading to cerebral oedema. In chronic liver disease, the accumulation of intracerebral glutamine is more insidious. Hence, astrocytes have time to equilibrate to these osmolar changes and cerebral oedema does not occur.

2. MASSIVE SYSTEMIC INFLAMMATORY RESPONSE

This leads to cerebral vessel vasodilatation and increased vessel permeability. This promotes the shift of intravascular fluid to the interstitial space, thereby leading to cerebral oedema. In chronic liver disease, the systemic inflammatory response is much less pronounced.

INVESTIGATIONS OF ACUTE LIVER FAILURE

All patients presenting with acute, severe hepatitis of uncertain aetiology should undergo screening for viruses, autoimmune antibodies and toxins, including serum ethanol and paracetamol levels, and have a Doppler ultrasound of their liver. Patients with established acute liver failure should have 6 to 8 hourly blood tests, namely full blood count, serum electrolytes, renal profile, clotting profile, liver enzymes including serum albumin, serum ammonia and arterial blood gases. Serum phosphate levels should be monitored daily as phosphate is consumed during liver regeneration leading to hypophosphataemia. Since these patients are susceptible to infections, they should have regular blood, urine and sputum cultures.

MANAGEMENT OF ACUTE LIVER FAILURE

1. ORTHOTOPIC LIVER TRANSPLANT

Without liver transplantation, the prognosis is very poor in acute liver failure. Hence a hepatologist should be involved immediately,

even if the patients do not seem sick enough initially. These patients deteriorate very fast and may miss the therapeutic time window for surgery. There are no universal, exclusion criteria for liver transplantation. However, many specialised centres agree that patients who are very unstable (overt septic shock with multi-organ failure), have uncontrolled seizures or signs of impending brainstem herniation (fixed, dilated pupils or posturing movements) or have malignancies outside the liver will not benefit from liver transplantation.

The American Society for Study of Liver Diseases has recommended the King's College Criteria in assessing the need for liver transplantation in patients with acute liver failure. According to the King's College Criteria, cases of paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. pH < 7.3; or
2. INR > 6.5, serum creatinine > 300 μmol/L and Grade III/IV encephalopathy.

According to the King's College Criteria, cases of non paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. INR > 6.5; or
2. Any 3 of the following: (a) age < 10 years or > 40 years; (b) aetiology - non-A, non-B hepatitis or idiosyncratic drug reaction; (c) duration of jaundice before encephalopathy > 7 days; (d) INR > 3.5; and (e) serum bilirubin > 300 μmol/L.

2. NEUROLOGICAL MANAGEMENT

The two most common neurological complications associated with acute liver failure are brain oedema and non-convulsive seizures. Intracranial haemorrhage due to coagulopathy is rare, but devastating when it occurs. All patients admitted with acute liver failure should have regular (30 minutes to 1 hourly) neurocharting. New, focal neurological deficits are more consistent with intracranial haemorrhage and warrant urgent CT brain. Symmetrical neurological deterioration with no focal deficits is more consistent with cerebral oedema. EEG is warranted in cases of neurological deterioration which cannot be explained by CT brain findings to exclude non-convulsive seizures, which would require treatment with intravenous anticonvulsants.

Brain oedema manifests clinically as severe confusion, somnolence and coma. Hence, all patients exhibiting any of these symptoms benefit from protective measures to restore cerebral perfusion, namely:

a. Measures to decrease brain oedema[1] including:
   i. Hyperosmolar therapy with hypertonic saline or mannitol aiming for serum osmolarity of 310-320mOsm/L;
   ii. Renal replacement therapy to lower serum ammonia to < 60 μmol/L even in the absence of renal failure, as ammonia is cleared by dialysis;
   iii. Intubation and hyperventilation, aiming for $PaCO_2$ (arterial partial pressure of carbon dioxide) of 35mmHg. Cerebral blood flow is directly related to $PaCO_2$ up to certain limits. Hence, by decreasing $PaCO_2$, cerebral blood flow is reduced. Therefore, patients with clinical manifestations of intracranial hypertension benefit from intubation and controlled, mechanical ventilation even if their Glasgow Coma Scale > 8 and they are still able to protect their airway
   iv. Hypothermia, aiming for a core temperature of 35°C as this leads to cerebral vessel vasoconstriction and subsequent reduction of intracranial pressure.
b. Measures to promote cerebral venous drainage, namely head of bed elevation 30°, maintaining the head of intubated patients in the neutral position and avoiding any constrictive ties around the neck to fix the endotracheal tube.

3. CARDIOVASCULAR SUPPORT

Patients with acute liver failure typically have high cardiac output states and vasoplegia. Noradrenaline is the vasoconstrictor of choice to counteract the vasoplegia. Restrictive fluid measures are usually desired to avoid worsening of cerebral oedema. These patients are prone to infections and septic shock as they are immunocompromised. Therefore, in case of non-improving clinical picture, broad spectrum antibiotics and antifungals should be considered early.

4. MANAGEMENT OF COAGULOPATHY

Coagulopathy is not corrected unless INR > 6 as it is a useful prognostic marker. Beyond this level, transfusion of fresh frozen plasma is indicated due to increased risk of spontaneous intracranial bleeding.

5. METABOLIC HOMEOSTASIS

Hypoglycaemia is common in acute liver failure as the hepatic glycogen stores are depleted. In such cases, hypertonic dextrose infusions should be used. 5% dextrose should be avoided as it worsens cerebral oedema.

6. N-ACETYLCYSTEINE INFUSION

In paracetamol overdose, hepatotoxicity occurs due to depletion of the hepatic glutathione stores. N-Acetylcysteine replenishes this hepatic glutathione. N-Acetylcysteine is also beneficial in non-paracetamol-induced acute liver failure as it has anti-oxidant properties and improves haemodynamics. In both cases, N-Acetylcysteine infusion should be commenced immediately and continued until discharge from intensive care or liver transplantation is performed.

CONCLUSION

A multimodal approach to the management of acute liver failure addresses the individual pathophysiological processes that occur in this condition. It improves chances of survival in patients awaiting liver transplantation and dramatically reduces the risk of death from neurological complications.

REFERENCE

1. Warrillow S, Bellomo R. Intensive Care Management of Severe Acute Liver Failure. In: Vincent JL (Editor) Annual Update in Intensive Care and Emergency Medicine. London: Springer; 2015. p. 415-430.

Relvar Ellipta is for patients (≥12 years) in need of asthma maintenance therapy[1]

Asthma

Because I simply don't have space for asthma

For patients like Maria, every day is full on, so even small reminders of asthma can have an impact. So, when they're uncontrolled on ICS alone, choose new Relvar Ellipta:

- The first ICS/LABA combination to deliver continuous 24-hour efficacy[2]
- In a practical, once-daily dose[1]
- Delivered in an easy to use device that patients prefer to their current inhaler[3,4]*

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** *The 92 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. *The 184 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting $beta_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. *For COPD:* One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** *Hypersensitivity* to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** ***Pregnancy:*** No adequate data available. ***Lactation:*** insufficient information available. ***Fertility:*** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 *micrograms/ 22 micrograms inhalation powder, pre-dispensed*. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom **Marketing Authorisation Numbers:** EU/1/13/886/001-6 **DATE OF PREPARATION:** December 2013

In order to ensure that this product information reflects the mos up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

REPORTING ADVERSE EVENTS (AEs):

Malta & Gibraltar: **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Malta: **alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system**

Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: **alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA):** https://yellowcard.mhra.gov.uk/

*Patients' current or previous maintenance inhalers: HandiHaler/ DISKUS/ MDI/ HFA (COPD); DISKUS/ MDI/ HFA (asthma).[4]

References: 1. Relvar Ellipta Summary of Product Characteristics. GlaxoSmithKline; 2013. **2.** Bleecker ER *et al.* Fluticasone furoate/vilanterol 100/25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *JACI In Practice* 2013 (in press). **3.** Svedstater H *et al.* Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FF/VI) and FF alone in asthma. ERS. 2013. **4.** Woepse M *et al.* Qualitative assessment of a two-strip dry powder inhaler (ELLIPTA™) for COPD and asthma. EAACI. 2013.

MLT_GIB/FFT/0003/16 Date of preparation: February 2016

gsk

Theravance

DID YOU KNOW?

GERMAN MEASLES – WHY *GERMAN*?

German measles is also known as rubella, which is derived from Latin, meaning 'little red.' Rubella was initially considered to be a variant of measles or scarlet fever and was called '3rd disease'. It was not until 1814 that it was first described as a separate disease in the German medical literature, hence the common name *'German measles'*. The virus is an enveloped, positive-stranded RNA virus classified as a Rubivirus in the Togaviridae family.

In 1914, the American physician Alfred Fabian Hess postulated a viral etiology for German measles based on his work with monkeys. The Japanese scientists S. Tasaka and Y. Hiro in 1938 confirmed the viral etiology by passing the disease to children using filtered nasal washings from persons with acute cases.

Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first published recognition of congenital rubella syndrome (CRS). Rubella virus was first isolated in 1962 by Parkman and Weller. The first rubella vaccines were licensed in 1969.

Rubella became notifiable under Maltese law in 1978, and legal provisions for the vaccination of girls between 10 and 13 years of age were mandated in 1989. Although CRS became notifiable in Malta in August 1990, only two cases were notified to the Department of Public Health till 1996.

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MPSA

MENTAL HEALTH

Renita Busuttil

"The mentally ill frighten and embarrass us. And so we marginalize the people who most need our acceptance. What mental health needs is more sunlight, more candor, more unashamed conversations"
[Glenn Close, American actress, b. 1947]

Our society is changing at a very fast rate, however unfortunately, some of our attitudes are stuck to our roots. Mentally ill people are stereotyped and often discriminated against. Many people are woefully misinformed about mental health and thus it has become surrounded by ignorance, prejudice and fear.

The impact of stigma is twofold. Social stigma refers to prejudicial attitudes and discriminating behaviour towards individuals with mental health problems as a result of the psychiatric label they have been given, e.g. passing a negative remark about one's mental condition and treatment. Subtle discrimination involves the avoidance of a person suffering from mental illness because it is assumed that the patient could be unstable. Self-stigma is the internalizing thoughts and silent fears which mental health sufferers go through due to their own perceptions of discrimination and perceived stigma, turning against themselves.

Therefore these patients are challenged doubly as they struggle with both the symptoms and complications that result from the disease and also the stereotypes and judgement that result from public humiliation and misconception about mental illness. This adds a greater burden, heavier to carry than the mental condition itself.

Mental illness can afect anyone, in different ways. The stigma and discrimination associated with mental health can be the hardest parts of the overall experience. Hence, we need to make a change in our daily judgemental comments and change them into positive vibes which bring happiness and courage to one another as one can never know what a person is going through.

59% of children wake at night due to their asthma[1]

Seretide® Evohaler®
50 mcg from 4 years[3]

Poppy is **50%** less likely to wake at night when using Seretide compared to baseline[2]

Seretide® Diskus®
100 mcg from 4 years[4]

Help Poppy by prescribing Seretide

Seretide is the only ICS/LABA proven to achieve guideline-defined asthma control in children[2]

Safety Information

Very common side effects: Headache and nasopharyngitis.
Common side effects: Candidiasis of mouth and throat, pneumonia, bronchitis, hypokalaemia and hoarseness/dysphonia
Special warnings and precautions for use: Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids.
It is important that patients are reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained. Monitor height of children on prolonged inhaled steroid therapy.

Seretide™ (salmeterol xinafoate and fluticasone propionate)
Kindly refer to full Summary of Product Characteristics (SPC) before prescribing.
Abridged prescribing information. Presentations: For Malta and Gibraltar: *Seretide Diskus* – Each dose provides 50 microgram salmeterol xinafoate and 100 microgram, 250 microgram or 500 microgram respectively of fluticasone propionate. *Seretide 50 Evohaler* - Each dose provides 25 microgram salmeterol xinafoate and 50 microgram of fluticasone propionate. For Gibraltar only: *Seretide 125,250 Evohaler:* Each dose provides 25 microgram salmeterol xinafoate and 125 microgram or 250 microgram of fluticasone propionate. **Therapeutic Indications:** For Malta and Gibraltar: *Seretide Diskus and Evohaler:* is indicated in the regular treatment of asthma where use of a combination (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate. *Seretide Diskus* is indicated for the symptomatic treatment of patients with COPD with a FEV_1<60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. *Seretide 50 Evohaler* is used in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist. For Gibraltar only: *Seretide 125, 250 Evohaler:* is indicated in the regular treatment of asthma where use of a combination (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate. Used in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist. **Dosage and administration:** Seretide is for inhalation use only. ***Seretide Diskus:*** Asthma – Adults and adolescents 12 years and over: one puff twice daily of Seretide 100 or Seretide 250 or Seretide 500 (each containing 50 mcg of salmeterol xinafoate and 100 mcg, 250 mcg or 500 mcg respectively of fluticasone propionate). Patients should be given the strength of Seretide containing the appropriate, lowest fluticasone propionate dosage for the severity of their disease. A short term trial of Seretide may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is one inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important. Seretide is not intended for the initial management of mild asthma. Seretide 50/100 micrograms strength is not appropriate in adults and children with severe asthma. Children 4-11 years: Seretide 100 Diskus (50 mcg salmeterol and 100 mcg fluticasone propionate) – one puff twice daily. ***Seretide Diskus:*** COPD: Seretide 500 Diskus (50 mcg of salmeterol xinafoate and 500 mcg fluticasone propionate) – one puff twice daily. ***Seretide 50 Evohaler:*** Adults and children 4 years and older: Two inhalations twice daily. For Gibraltar only: ***Seretide 125, 250 Evohaler:*** Adults and adolescents 12 years and older: Two inhalations twice daily. **Contra-indications:** Hypersensitivity. **Warnings and Precautions:** Seretide should not be used to treat acute asthma symptoms for which a fast- and short-acting bronchodilator is required. Patients should not be initiated on Seretide during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related events and exacerbations can occur during Seretide therapy; sudden and progressive deterioration in control or increased use of bronchodilator therapy warrants urgent medical assessment especially in patients of African-American origin (SMART). As with all inhaled medication containing corticosteroids, Seretide should be administered with caution in patients with pulmonary tuberculosis, severe cardiovascular disorders, including heart rhythm abnormalities, diabetes mellitus, untreated hypokalaemia/patients predisposed to hypokalaemia or thyrotoxicosis. In case of paradoxical bronchospasm discontinue Seretide, assess patient and give alternative therapy if necessary. Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods, but are less likely than with oral steroids. It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained. Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crises. Rarely, a range of psychological or behavioural effects such as psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) may develop on prolonged use. Monitor height of children on prolonged inhaled steroid therapy. Transfer from oral steroids: Special care needed. Monitor adrenal function. Consider appropriate steroid therapy during periods of stress or elective surgery. Ritonavir can greatly increase the concentration of fluticasone propionate in plasma, therefore avoid concomitant use. There is also an increased risk of systemic side effects with other potent CYP3A inhibitors. There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in the TORCH study in patients with COPD receiving Seretide compared with placebo; older patients, patients with a lower body mass index (<25kg/m^2) and patients with very severe disease (FEV_1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. **Drug Interactions:** Avoid beta-blockers. Concomitant use with other beta-adrenergic containing drugs can have a potentially additive effect. Potent CYP3A4 inhibitors: Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 mcg inhaled twice daily) resulted in a significant increase in plasma salmeterol exposure which may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone. The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir). **Pregnancy and Lactation:** Experience limited. Balance risks against benefits. **Undesirable effects:** *Very Common/Common* - candidiasis of mouth and throat, pneumonia, bronchitis, hypokalaemia, headache, hoarseness/dysphonia, throat irritation (uncommon with Seretide 50 Evohaler), nasopharyngitis, sinusitis, contusions, traumatic fractures, arthralgia and myalgia, muscle cramps (uncommon with Seretide 50 Evohaler). See SPC for information on all adverse events. **Overdose:** *due to Salmeterol*: tremor, headache, tachycardia; *due to Fluticasone propionate:* temporary adrenal suppression.
MA Holder (Malta): GlaxoSmithKline (Ireland) Ltd. Trading as: Allen & Hanburys Ltd. **MA Numbers (Malta):** *Seretide Diskus:* MA 192/00901-3; *Seretide 50 Evohaler:* AA 192/00904. **Legal category**: POM. Not all pack sizes may be marketed. Date of revision of text: August 2013.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

REPORTING ADVERSE EVENTS (AEs):
If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131) or e-mail: mt.info@gsk.com
Malta: any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:
Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt
Gibraltar: any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

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2. DeBlic J *et al. Pediatr Allergy Immunol* 2009: 20:763–771
3. Seretide Evohaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.
4. Seretide Accuhaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.

Date of Preparation: **January 2015** ZINC CODE: **MLT_GIB/SFC/0002/15**

SERETIDE®
salmeterol/fluticasone propionate

MEDICAL RESEARCH IN THE MOVIES: 'LIVING PROOF'

MICHELLE MUSCAT

Director: Dan Ireland
Writer: Vivienne Radkoff (movie), Robert Bazell (book)
Stars: Harry Connick Jr., Tammy Blanchard, Amanda Bynes
Runtime: 125 min
Release Date: 2008

Living Proof is a medical TV drama based on a true story. It revolves entirely around the clinical trials and tribulations of development of Herceptin®, including the struggles of some of the women enrolled in the initial single dosage exploratory 'mouse protein study' and Phase I-III trials. It provides very valid medical insights into the potential hardships of medical research, funding required for laboratory equipment, and recounts a development that proved to be a milestone in the treatment of HER-2 (Human epidermal growth factor receptor 2) positive breast cancer patients.

Trastuzumab, or as it is better known, Herceptin®, is a monoclonal antibody drug used to treat HER2-positive breast cancer and HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction by targeting the HER-2/neu receptor.[1-5] One of the opening scenes of the movie takes place in Dr Dennis Slamon's laboratory, at the UCLA Medical Center in the US, where we are introduced to the protagonist and his new assistant. We are also presented to the individual lives of different women and their families, who are later diagnosed with breast cancer. The movie proceeds to introduce the audience to the various phases of drug development. The biotechnology manufacturer of Herceptin®, Genentech Inc., repeatedly referenced in the film, is seen in the movie to develop the drug jointly with Dr Slamon from UCLA. The complete drug developmental milestones in the real life story are somewhat more comprehensive, and also included other named scientists as well, responsible for contributing in various ways to the final breakthrough.

In parallel, we see one of the patients, diagnosed with breast cancer, being presented with the standard options of mastectomy, chemotherapy and radiation, which is what had been previously offered to her mother. Dr Slamon faced numerous challenges throughout the course of the research studies, including initial funding issues as well as personal hardships. In the Phase I trial, cisplatin was used in combination with Herceptin®. Nicole, who had stage 4 cancer was the first patient to originally receive the drug during, what is called in the movie, the initial exploratory 'mouse protein study'. This involved a single dose to test for tolerance in humans. However, she did not meet the eligibility requirements defined by the protocols for Phase I, and was hence not included in spite of the efforts by her relatives.

In the movie we see that the supraclavicular lump of a patient, enrolled in Phase 1, noticeably decreases in size. On the other hand, one of the patients passes away due to her advanced cancer. These situations proved to be an emotional roller coaster for the cohort. Not all Phase I patients moved forward to Phase II, given the stringent Food and Drug Administration (FDA) standards for inclusion. During Phase III trials, the National Breast Cancer Coalition advocates were involved to allow compassionate access to the drug for the women who do not qualify for the trial. Towards the end of the movie, during the Revlon Run/Walk for women, Dr Slamon meets the relatives of some patients. The movie ends with the approval of Herceptin® by the FDA, which happened in 1998.

Although not shown in the movie, but directly related to the chemical pathology field of the author, a trastuzumab assay has later also been developed for the bioanalytical quantification of trastuzumab levels in blood.[6-7]

This review is partially funded through the Endeavour Scholarship Scheme.

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MARIKA AZZOPARDI

50 YEARS OF SKIN SCRUTINY

Addressing the General Assembly of the World Medical Association in Stockholm

PROFESSOR JOSEPH PACE IS A VETERAN DERMATOLOGIST WHO HAS SEEN HIS FAIR SHARE OF SKIN CONDITIONS. IN THIS INTERVIEW, HE SHARES SOME INSIGHT INTO HIS CAREER, HIS RESEARCH AND HIS JOYS IN LIFE.

TS: HOW LONG HAVE YOU BEEN A MEDICINE MAN?

Next year I look forward to celebrating 50 years as a doctor. Over these years I have worked in Edinburgh, Manchester, Stoke-on-Trent, in Saudi Arabia, and of course in Malta. Here in Malta apart from my private practice which keeps me busy now, I held varied posts in the past including Chair of the Dermatology Department at Boffa Hospital and in the Faculty of Medicine from 1987-1990. I have also been President of the Medical Association of Malta, President of the World Medical Association, Chairman of the First EADV Spring Meeting held in Malta, and also President of the Foundation for Medical Services. I have been Secretary General of the European Academy of Dermatology for six years. Outside Europe I am Visiting Clinical Professor of Dermatology at Jefferson Medical Centre of Thomas Jefferson University in Philadelphia, and also a Fellow of the American Academy of Dermatology and the American Dermatology Association (ADA) besides being an Honorary member of several national Dermatology societies.

TS: WHY DERMATOLOGY?

Why I chose dermatology is a good question when the UK training system gives ample grounding in all medical sub specialities. I was fortunate to do Dermatology as a core part of my general medical training with consultants who emphasised on a daily basis that being a good dermatologist requires thorough grounding in both primary skin disease as well as internal diseases that cause changes to the skin. This made a lot of sense and it needed only a suggestion from my mentor Eric Donaldson to persuade me to give Dermatology a try! It seems to have worked out and I have seen the speciality move from Cinderella status to a highly scientific cutting edge discipline which attracts the best graduates in Malta and seemingly in every country I know.

TS: WHAT SKIN CONDITIONS HAVE INCREASED OVER THESE YEARS?

Skin cancer and female adult acne. Everyone is or should be knowledgeable about skin cancer but in the past the latter was practically unheard of, indeed considered most unusual!! Today we see so many women in adulthood, suffering from what looks like teenage acne... and it may be linked to cysts in the ovaries (PCOS). If left untreated, this condition can have serious repercussions on other health issues. So the first alarm bell when a patient presents with adult acne is to consider possible PCOS. This condition can now be tackled from a young age, of great importance considering that patients with ovarian cysts may be prone to diabetes and heart disease.

TS: WHAT ARE THE KNOWN CAUSES OF THIS?

Stress is a major trigger, in adult acne as also in psoriasis and eczema. This skin condition causes enormous psychological damage. People think it is contagious, which it is not. This is in actual fact a hereditary condition which does become aggravated in stressful periods of life. In Malta, we unfortunately, (and some would say very unfairly) have a very ambiguous situation associated with support for manifestly chronic skin conditions. The Schedule 5 system rightly supports free medicines for chronic diseases. The problem is that it discriminates between equally chronic conditions and thus between equally affected and equally tax contributing Maltese citizens. Thus eczema patients get zero support while psoriasis patients get full support, in spite of both conditions seriously affecting *Quality of Life* confirmed objectively in numerous studies to be equal or worse than patients with chronic kidney and heart disease! There are many new treatments on the market, which, if made available, could alleviate much suffering for patients, including children, who may or may not be able to afford expensive treatment often for many years on a daily basis.

TS: HOW HAS MEDICINE CHANGED OVER THESE YEARS SINCE YOU GRADUATED?

I still remember when I became a doctor, we were still boiling needles. There were very few young doctors at the time. Now the hospital has large numbers of young doctors working within it. The modes of practise have changed completely - for one thing, the systems are all digitized now, including patients' data. The hardware, the techniques … so much has transformed medicine. However, we must never forget the dictum of the late Professor Ganado who referred to *His Majesty the patient* or that of the Knights of Malta - *Our Lords the Sick.*

TS: WHEN YOU ARE OUT AND ABOUT DO YOU EVER STOP AND NOTICE PEOPLE WITH TERRIBLE OR POSSIBLY DANGEROUS SKIN CONDITIONS AND WOULD YOU POINT IT OUT TO THEM?

It is very difficult because yes, I do notice people with skin cancer or terrible acne. Some things just jump to attention for somebody like myself who has been treating skin problems for so long especially if these can be improved. One has to be very careful not to alarm people, and not to interfere with their privacy. However, there have been situations where I could not fail to note a dangerous skin lesion, in which case I did throw a very diplomatic hint that it would be wise to have it seen to sooner rather than later.

Saadah Yemen - a picnic with friendly tribesmen. The AK47 had its safety catch on OFF, I found out later

American Congress of Dermatology in Venezuela

Mentor and great friend George Csonka in Syria in 1953 with WHO mission

Examining the effects of the sauna environment on the skin in Lapland

Showing a Chinese delegation the plans of Mater Dei hospital

TS: WHAT DO YOU DO WHEN YOU ARE NOT TREATING PATIENTS?

I have been deeply involved in medical politics both here and abroad. I have a very full family life which includes five grandchildren, who I refer to as a lovely granddaughter and four terrorists! Everybody knows that I am a football fan … actually an ardent Juventus football fan who at long last this year managed to obtain a season ticket and saw 12 games, all wins: what an experience.

TS: HOW DID THIS LOVE FOR THE JUVENTUS TEAM COME ABOUT?

I always liked the team, was always a fan. 30 years ago I was in Brussels to attend the European Cup Final between Juventus and Liverpool. It was the 29 May 1985, a date I will never forget. So many Juve fans died or were injured when a wall collapsed in the Heysel Stadium. I was there with the crowd and well … after something like that, the bond only became stronger. It is incredible that one dies at a football match.

I READ THE SYNAPSE BECAUSE...

perhaps it is the only way to keep up with local happenings although the editor rightly steers clear of controversy. He does a great job and has a great team …

Just last month, Jane was a prisoner in her own home.

Serotonergic antidepressants insufficiently address the core depressive symptoms associated with "Decreased positive affect"[1]

Loss of pleasure, Loss of interest, Fatigue, Loss of energy

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.

WELLBUTRIN XR – Abbreviated Prescribing Information: ***Please refer to full Summary of Product Characteristics (SmPC) before prescribing.*** **TRADE NAME:** Wellbutrin XR modified release tablets. **COMPOSITION:** Buproprion Hydrochloride 150 mg and 300 mg. **INDICATIONS:** Treatment of major depressive episodes. **POSOLOGY AND METHOD OF ADMINISTRATION:** Wellbutrin XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures. *Adults:* The recommended starting dose is 150 mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300 mg once daily. There should be an interval of at least 24 hours between successive doses. *Children and Adolescents:* Not indicated for use in children or adolescents aged less than 18 years. *Elderly Patients:* Same as adults but with greater sensitivity in some elderly individuals. *Hepatic and renal impairment:* 150 mg once a day. *Discontinuing therapy:* A tapering off period may be considered. *Overdose:* Symptoms including drowsiness, loss of consciousness and/or ECG changes and rarely deaths even with large overdoses. **CONTRAINDICATIONS:** Hypersensitivity to buproprion or any of the excipients; co-administration with other medicinal products containing buproprion as the incidence of seizures is dose-dependent; current seizure disorder or history of seizures; known CNS tumor; withdrawal from alcohol or any medicinal product known to be associated with the risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **SPECIAL WARNINGS AND PRECAUTIONS:** Do not exceed the recommended dose of Wellbutrin XR especially in patients who have predisposing factors for seizures since the risk of seizures is dose-related. Not recommended/discontinued in patients who experience a seizure during treatment. Careful monitoring during the first weeks of treatment/dose changes/in patients with history of suicide-related events prior to treatment; discontinuation should be considered in cases of severe and sudden onset of suicidal ideation/behaviour. Wellbutrin XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment; Use with caution in patients with hepatic and renal impairment. **INTERACTIONS:** Concomitant use with MAOI's is contraindicated; The dose of certain antidepressants, anti-psychotics, beta-blockers, SSRI's and Type 1C antiarrhythmics should be reduced when given concomitantly with Wellbutrin XR; Use with caution with cyclophosphamide and ticlopidine, carbamezapine, phenytoin, ritonavir, tamoxifen, valproate, levodopa or amantidine, alcohol and nicotine transdermal system. **ADVERSE EVENTS:** *Very Common:* Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting; *Common:* Hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe), flushing, abdominal pain, constipation, rash, pruritus, sweating, fever, chest pain and asthenia. *Not known:* suicidal ideation and suicidal behaviour. Refer to the SPC for a full list of adverse events. **PREGNANCY AND LACTATION:** Not recommended. **ABILITY TO DRIVE AND USE MACHINES:** Use with caution. **PRESENTATIONS:** Wellbutrin XR 150 mg and 300 mg x 30 tablets. **LEGAL CATEGORY:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, UK. **Marketing Authorisation Number:** MA 302/00101-2. **Date of preparation:** September 2013. **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).**

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Put depression behind them.

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Job No: MLT_GIB/BHC/0002/16 Prepared: March 2016

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The Noradrenaline & Dopamine Re-uptake Inhibitor.

MARK XEUREB

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION-

A REVOLUTIONARY TREATMENT FOR DEPRESSION AND OTHER DISORDERS

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe, painless, effective and natural evidence-based treatment for people suffering from severe unipolar affective/depressive disorder and other neurological/psychological illnesses. Used successfully in renowned centres such as the Mayo clinic, Johns Hopkins and the Nottingham Neuromodulation Unit,[1,2] rTMS is now available locally. This non-invasive FDA[3-5] and NICE[6] approved electromagnetic therapy is ideal for depressed patients who are either resistant or intolerant to other treatments. rTMS has no side-effects associated with drugs (e.g. weight gain, sexual dysfunction, sedation). Besides, no anaesthetic is involved and there is no memory loss or impaired learning as may happen with electroconvulsive therapy (ECT), which has long been considered the gold standard for treating such patients. rTMS is claimed to be more effective than medication,[7,8] psychotherapy or ECT[9-12] in treatment-resistant patients. Thankfully, rTMS has a synergistic effect when used with other treatments.

WHO states that there are 350 million depressed people worldwide. Depression is the leading cause of disability globally. When coupled with other co-morbid illnesses, it has a lifetime prevalence of 23%.[13]

The hidden psychological and social burden inherent to depression causes many to suffer in silence, potentially leading to suicide. Furthermore, for every person who commits suicide there are at least 20 others who try.[14] rTMS can give relief to these people, prevent deaths and offer hope to those suffering from e.g. migraine, ADHD, altered body image, OCD.

rTMS is the brainchild of Baker and his colleagues who began experimenting in the 1980s. Inspired by Galvani and Aldini's eighteenth century experiments on electrically stimulating the peripheral muscles of dead animals and corpses respectively, the UK team pioneered the stimulation of the human brain's motor homunculus electromagnetically. Their objective at the time was to elicit a corresponding motor stimulation of peripheral muscles.[15]

In 1987, Bickford extended the domain of TMS research into neuropsychiatry. He described transient mood elevation in healthy subjects receiving single-pulse stimulations to the motor cortex.[16] This was the turning point for the scientific investigation of the effects of depolarising magnetic fields in a variety of neuropsychiatric disorders.

Technological developments produced repetitive-pulse TMS which was shown to have long lasting effects on the cortex that persisted beyond the stimulus delivery.[17-19] Once it was ascertained that rTMS technology could stimulate the brain in a focal way, the search was on to use this technique to treat neuropsychiatric disorders, with the earliest studies attempting to treat depression.[20-22]

This novel treatment is based on the discoveries of British nineteenth century physicist Michael Farady, whose Law of Electromagnetic Induction predicts how a changing magnetic field will interact with an electric circuit to produce an electromotive force - a phenomenon called electromagnetic induction.

The painless electromagnetic therapy coil is applied to the patient who sits comfortably in a chair

In essence, exposing a conductor to a rapidly changing magnetic field will induce a current in the conductor. rTMS works by inducing a rapidly changing magnetic field in a "depression sensitive" brain/cortical area, which is populated by neurons and is located just under the skull. This rapidly changing field induces a current in the neurons (the conductor). Hence, the area is stimulated to be more electrically active.

In biophysiological terms, several studies show that the left dorso-lateral pre-frontal cortex (LDLPFC), along with deeper cortical structures such as the limbic system, is associated with mood regulation and hence is a lynchpin in the pathogeneses of depressive illness. Overall, a depressed brain is less active than a healthy brain, as evidenced by several neuroimaging studies. It also has fewer brain receptors, less circulating neurotransmitters (e.g. serotonin) and fewer healthy nerve contacts (synaptic connections between neurons).[23]

rTMS addresses this neuronal "apathy" by progressively re-stimulating a current in the LDLPFC neurons (i.e. a wave of depolarisation down the neuron membranes) so as to eventually restore the balance of neurotransmitters and healthy nerve contacts. The positive behavioural effects of this technology persist after a course of rTMS treatment.[24,25]

NICE "noted consistently positive outcomes in many studies" and explained that rTMS has "a good safety profile". Besides, "commentary from patients was positive and described significant benefits to their quality of life, including the advantages, for some patients, of being able to stop the use of oral antidepressant medications".[6]

In essence, the patient is seated in a comfortable chair as an electromagnetic field is applied over the LDLPFC for up to 37 minutes. Patients remain fully alert throughout: no anaesthetic, medicine or invasive procedure is required. During the session, the person can talk, read or watch TV. He can even undergo psychotherapy. Once done, the patient simply hops off the chair and carries on with his day.

If your patients feel life is not worth living, please reassure them that it is! However, they may be going through a crisis. We can help. . Call us on our 24/7 crisis line (99339966), email us (crisismalta@gmail.com) or get help from our *Crisis Resolution Malta* FaceBook page.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

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IMAGING THE CERVIX PART I

PIERRE VASSALLO

During pelvic ultrasound (US), the examiner consistently reports findings in the uterine body, endometrium and adnexa, while the cervix is often not mentioned. This probably results from a training in transabdominal pelvic US, since the cervix is poorly seen with this technique. On the other hand, endovaginal pelvic US with the excellent image quality obtainable on new devices, allows detailed assessment of the cervix.

Endovaginal US can visualize the cervix in both the long axis and the short axis. The long axis lies parallel to the cervical canal, which extends from the internal os to the external os. In the long axis of the cervix, a central echogenic line is seen that correlates with the apposed surfaces of the anterior and posterior mucosal (or glandular) layers that line the cervical canal.
A small amount of fluid may be present within the cervical canal particularly in the periovulatory period. The mucosal layer, which lines the cervical canal, is iso- to hyperechoic and measures 2-4mm in thickness. Surrounding the mucosal layer is the stromal layer, which is moderately echogenic and forms the bulk of the cervix. Between the mucosal and stromal layer, a thin 1-2mm hypoechoic line may be seen that represents the submucosal layer (Figure 1).

Endovaginal US in the short axis shows the cervix as round or oval, containing a central echogenic spot representing the cervical canal surrounded by an iso- to hypoechoic mucosal layer, which is in turn surrounded by the echogenic stromal layer. Frequently, folds may be seen in the mucosal layer that represent the plicae palmatae (Figure 2).

Magnetic resonance imaging (MRI) allows the best visualization of the cervix and is used to characterize indeterminate US abnormalities. MRI is the gold standard for staging cervical cancer. On T2-weighted images, the cervix shows a distinctive trilaminar appearance, with an innermost hyperintense layer measuring 3–8 mm that corresponds to

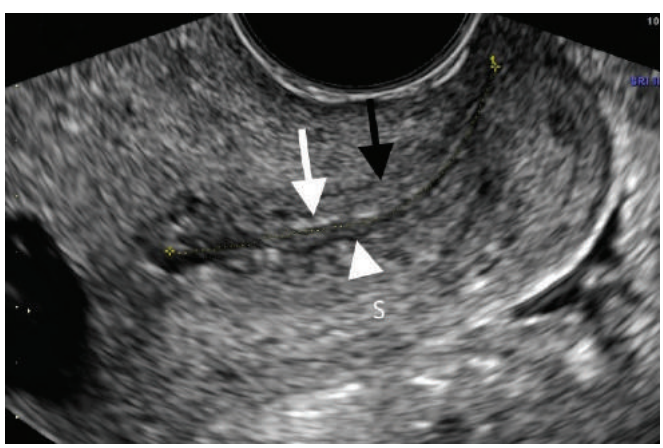


Figure 1. Endovaginal US scan in the long axis of the cervix at 15-week gestation showing a central echogenic line that represents the apposed surfaces of the cervical mucosa (white arrow), surrounded by the mucosal layer (black arrow) and stromal layer (S). A thin hypoechoic submucosal layer lies between the stromal and mucosal layers (arrowhead).

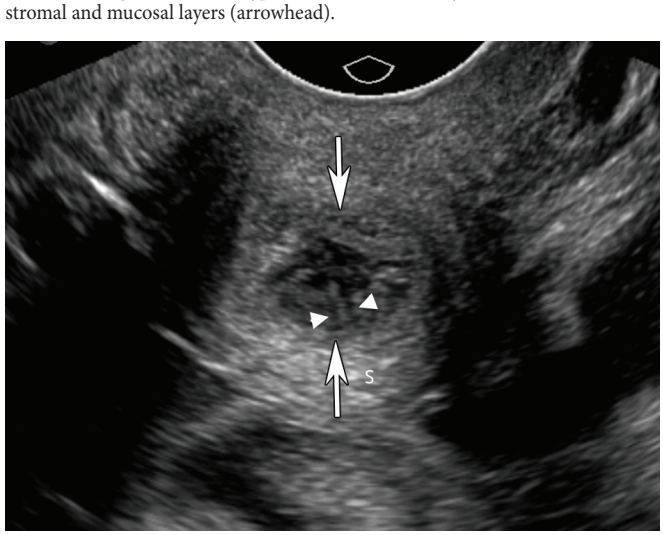


Figure 2. Endovaginal US scan in the short axis of the cervix showing the mucosal layer (arrows) and the stromal layer (S). Plicae palmatae are present in the mucosal layer (arrowheads).

mucosa and secretions, a middle low-signal-intensity layer representing the inner cervical stroma that measures 3–8 mm, and an outermost intermediate-signal-intensity layer representing the outer cervical stroma that measures 2–8 mm (Figure 3).

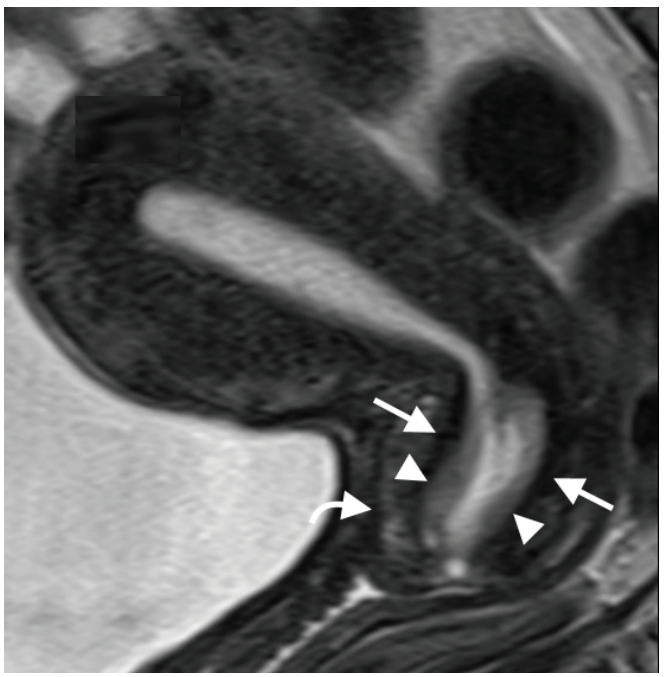


Figure 3. MRI scan of the cervix in longitudinal section showing the mucosal layer (arrowheads), the inner stromal layer (arrows) and the outer stromal layer (curved arrow).

CONGENITAL ANOMALIES

Congenital anomalies of the cervix are readily seen on US but are best demonstrated on MRI. One of the most common congenital anomalies is a septate uterus and cervix accounting for circa 45% of all congenital uterine anomalies. This results from incomplete fusion of the Müllerian ducts with persistence of an intervening septum. On US, it is best visualized in the coronal plane as a hypoechoic band extending from the uterine fundus into the cervix (Figure 4). The septum is composed mainly of fibrous stroma, which accounts for its hypoechogenicity. It shows increased vascularity on colour Doppler US in 70% of cases. MRI is the best imaging modality to evaluate a septate uterus and cervix; the fibrous septum is depicted as a low signal band extending from the flat uterine fundus into the cervix in the coronal plane (Figure 5). The septum may continue into the vagina in up to 25% of cases.

Uterus didelphys or "Double Uterus" represents a congenital anomaly where there is complete duplication of the endometrial cavity. The two endometrial cavities are separated not just by a fibrous septum as in a septate uterus but by a central stromal layer lined on either surface by mucosal layers. A uterus didelphys may contain two separate uterine cavities fusing into a single cervical canal or a fully duplicated cervix (Figure 6a). It may be difficult to distinguish a septate cervix from a duplicated

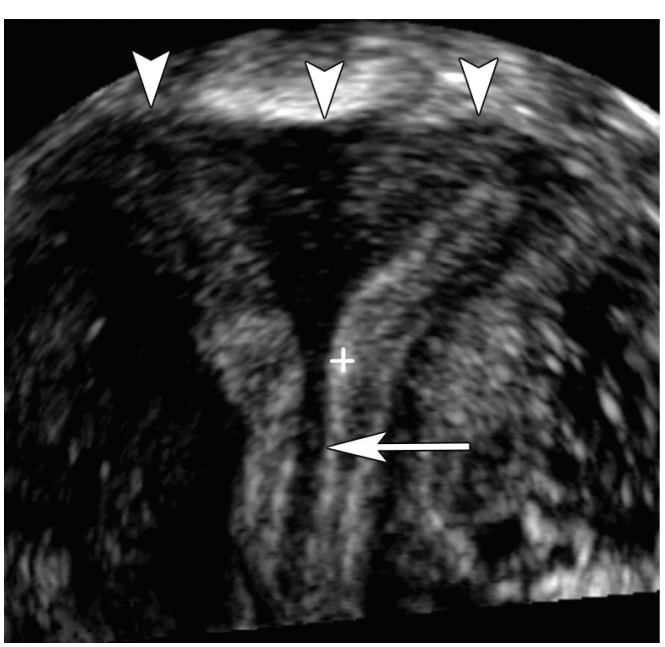


Figure 4. Coronal endovaginal US of the uterus and cervix showing a midline septum extending from the fundus (arrowheads) into the cervix (arrow). Note the flat shape of the fundus, a feature which is used to differentiate a septate from a bicornuate uterus (+internal os).

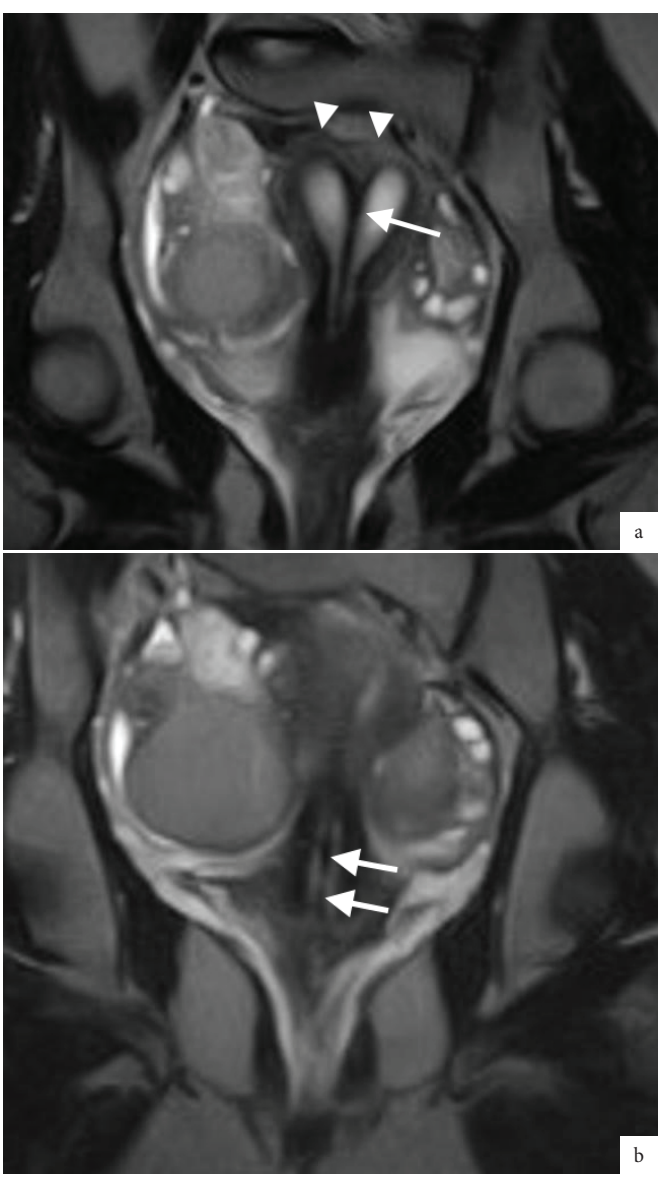
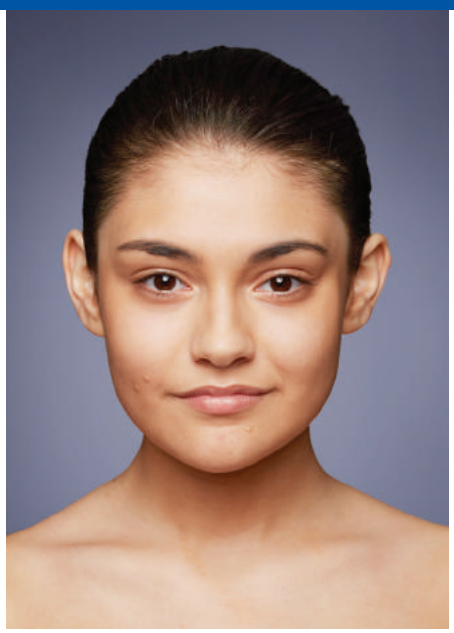


Figure 5. Coronal T2 weighted MRI images of the uterus (a) and cervix (a and b). A hypodense septum (arrows in a and b) extends from the flat fundus (arrowheads in a) into the cervix. Case courtesy of Dr Aneesh km, Radiopaedia.org, rID: 27061.

DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST[1,3]



DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

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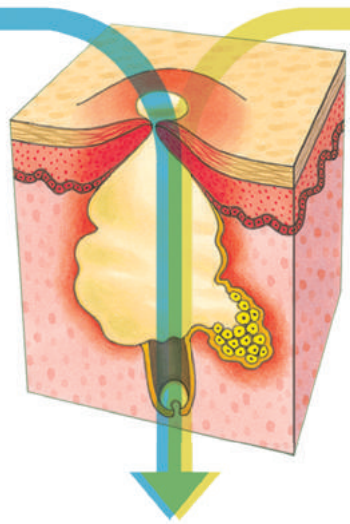
- Treats comedones[2] and inflammatory lesions[5]
- Bactericidal action against *P. acnes* strains[2]

Clindamycin

- Suppresses *P. acnes* [2]
- Anti-inflammatory action[5]



Duac:[2]
Unblocks follicles
Reduces inflammation
Kills bacteria
Reduces the potential for bacterial resistance

DUAC UNDERSTANDS WHAT'S IMPORTANT TO PATIENTS

- **Duac works fast, starting to work in just 2 weeks[3]**
- **Duac is a once daily treatment[2]**
- **Duac is generally well-tolerated[2,5]**

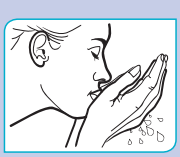
Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[1]

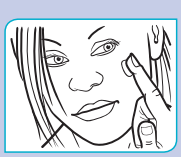
YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[4]: Once-daily, in the evening, your patients should[2]:



• Thoroughly wash the affected area of skin

• Gently pat dry



• Apply a thin layer of Duac gel on the affected area, not just the individual spots

TIPS[4]

If your patient's skin peels or becomes dry, they can try:
- Using an oil and fragrance-free hypoallergenic moisturiser
- Using Duac less often, or stopping for one or two days before starting again

Duac® Once Daily 10mg/g + 50mg/g Gel Abridged Prescribing Information

**Please refer to the full Summary of Product Characteristics (SPC) before prescribing*

Trade Name: Duac® Once Daily Gel. **Active Ingredients:** Clindamycin phosphate/ anhydrous benzoyl peroxide. **Pharmaceutical Form:** 10mg/g + 50mg/g gel. **Indication:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **Posology and Method of Administration:** Cutaneous use only. *Adults and Adolescents:* Once daily in the evening. Treatment should not exceed more than 12 weeks. *Elderly:* No specific recommendations. **Contraindication:** Hypersensitivity to active substances, lincomycin and any of the excipients. **Precautions for Use:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated /broken skin. Use with caution in patients with a history of regional enteritis, ulcerative colitis and antibiotic-associated colitis. If significant diarrhoea occurs or patients suffers from abdominal cramps, treatment should be immediately discontinued. *Resistance to clindamycin:* Patients with a recent history are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commmensal flora. *Cross-resistance:* May occur when using antibiotic monotherapy. **Fertility, Pregnancy and Lactation:** There is no adequate data. Avoid application of the product to the breast area. **Effect on Ability to Drive or Use Machines:** No studies. **Side Effects:** Very Common side effects (at least 1 in 10) include erythema, peeling and dryness. Common side effects (less than 1 in 10) include burning sensation, photosensitivity and headache. **Overdose:** No specific antidote. Treatment should consist of appropriate symptomatic measures or clinically managed. **Local Presentation:** 30g gel. **Marketing Authorization Holder:** GlaxoSmithKline UK Ltd., Trading as Stiefel. **Marketing Authorization Number:** MA 300/01401. **Legal Category:** POM. **Date of Preparation:** January 2016

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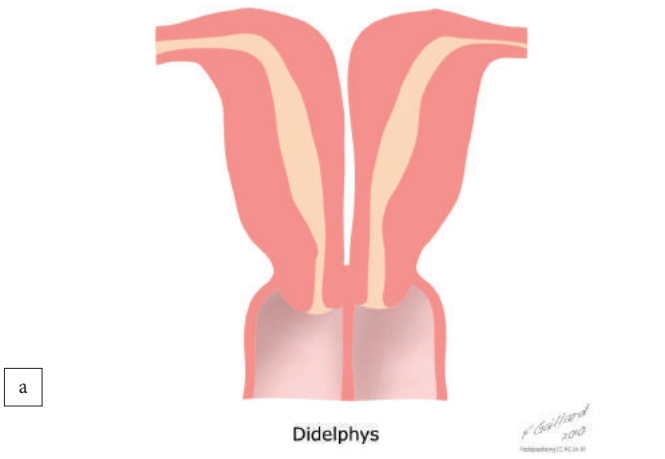
Gibraltar: **alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA):** https://yellowcard.mhra.gov.uk/

References: 1. Langner A *et al.* BJD 2008; **158**: 122–129. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Langner A *et al.* JEADV 2007; **21**: 311-319. **4.** Duac 5% Patient Information Leaflet, October 2014. **5.** Lookingbill DP *et al.* JAAD 1997; **37**: 590-595.

Stiefel
a GSK company

Duac® once daily gel
Clindamycin 1% and benzoyl peroxide 5%

Job no.: MLT_GIB/CBP/0002/15 Date of preparation: January 2016



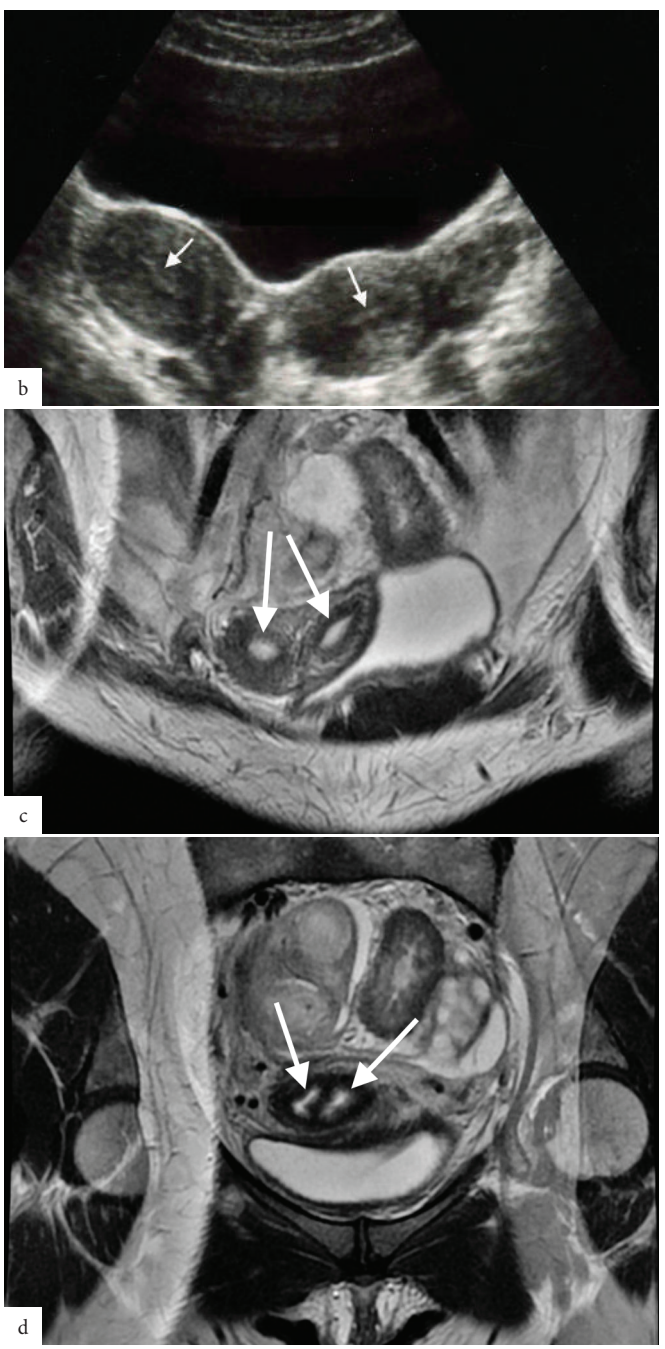


Figure 6. Diagram (a) showing a uterus didelphys with complete duplication of the cervix and a vaginal septum. US transverse scan (b) showing a duplicated uterine cavity (arrows). Short axis T2-weighted MR images showing duplication of the uterine cavity (arrows in c) and of the cervix (arrows in d) in a uterus didelphys. Case courtesy of Prof Frank Gaillard, Radiopaedia.org, rID: 11115.

cervix on ultrasound; in a duplicated cervix the band separating the two cervical canals is thicker that in a septate cervix (Figure 6b). Figures 6c and d illustrate separate endometrial cavities and cervical canals with a band of intervening stroma, clearly shown on MRI (Figure 6c and d).

CERVICITIS

Cervicitis is the term used to describe cervical inflammation, which may be acute or chronic. This is most often caused by infection, although trauma, pelvic radiation, chemical irritation, and sometimes malignancy may also cause cervical inflammation. Microorganisms such as *Trichomonas vaginalis*, *Candida albicans*, herpes simplex virus (especially type 2), *Neisseria gonorrhoeae* and *Chlamydia trachomatis* can also cause cervicitis. Patients usually present with purulent cervical and vaginal discharge and may complain of pelvic discomfort. US findings of cervicitis can be subtle or even completely occult, especially if the condition is of a chronic nature or if the patient is examined during or after effective antimicrobial treatment. At US, the cervix in patients with acute cervicitis shows a diffusely heterogeneous echotexture of the cervical mucosa and stroma (Figure 7a), with markedly increased vascularity on Doppler US imaging (Figure 7b). Hypervascularity can also be seen in cervical carcinoma, however in cervicitis, no mass lesion is seen. Cervicitis may lead to cervical canal stenosis and complex fluid collections within the cervical canal. Such fluid collections may mimic a cystic tumour in the cervical canal on US, however colour Doppler evaluation would confirm the avascular nature of the endocervical content (Figure 8).

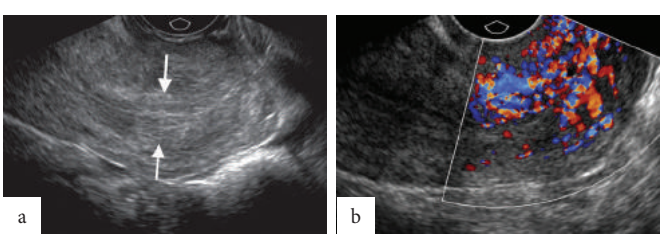


Figure 7. Sagittal US scans in a case of cervicitis showing heterogeneity of the mucosal layer (arrows in a) with marked hypervascularity on colour Doppler US (b).

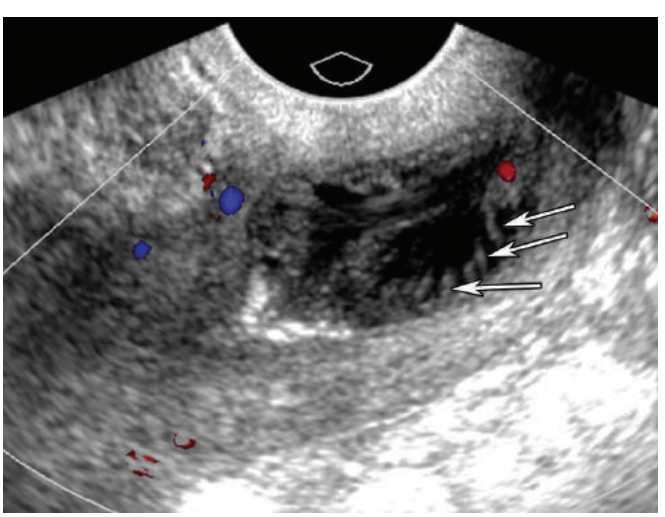


Figure 8. Sagittal US scan showing a complex fluid collection in the cervical canal; note the presence of plicae palmatie (arrows) as well as the absence of colour Doppler flow signal within the cervical canal.

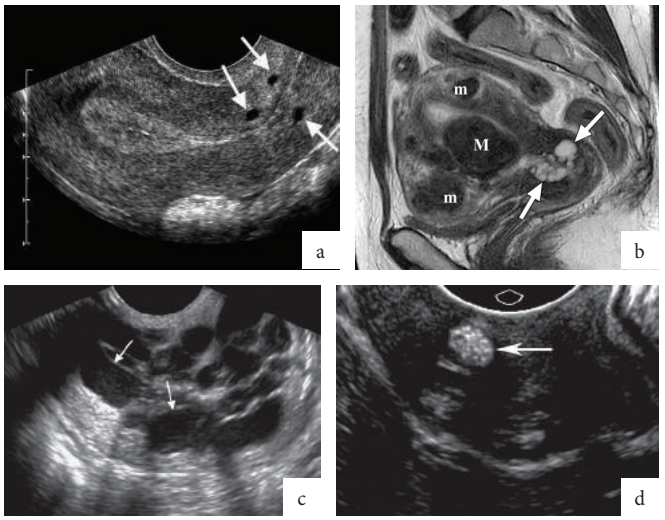


Figure 9a. Sagittal US scan of the cervix showing multiple small Nabothian cysts. b. Sagittal T2-weighted MRI scan of the uterus and cervix showing multiple Nabothian cysts (arrows) protruding into the stromal layer. Multiple fibroids (fibromyomas , M) are also present. c. Sagittal US scan through the cervix showing numerous Nabothian cysts with some containing echogenic material (arrows) indicating protein-rich fluid or intracystic haemorrhage. d. Sagittal US scan of the cervix showing crystalline deposits within a Nabothian cyst (arrow).

BENIGN UTERINE GROWTHS

Nabothian cysts are one of the most common findings on pelvic ultrasound. Nabothian cysts are mucus-retention or epithelial-inclusion cysts that arise from an obstruction of endocervical glands by proliferating squamous epithelium. They may or may not be associated with previous clinical or subclinical episodes of cervicitis. Nabothian cysts may appear as anechoic fluid collections in the mucosal layer of the cervical canal (Figure 9a), but can be quite large and protrude into the stromal layer (Figure 9b). They may also contain echogenic material due to secondary intracystic haemorrhage (Figure 9c) and even calcifications (Figure 9d).

Cervical polyps are the most common endocervical lesions and are also the most common cause for intermenstrual bleeding. They occur most commonly in women between the ages of 30 and 40 years of age and 25% are associated with an endometrial polyp. Cervical polyps appear slightly hyperechoic compared to the cervical mucosa on US (Figure 10a), they are seen to move on pressure with the endovaginal probe and are frequently noted to have a vascular pedicle on colour Doppler US (Figure 10b).

Cervical fibroids or fibromyomas are not uncommon and may lead to some diagnostic difficulty. They may also result in shoulder impaction during child birth. Cervical fibroids are seen as hypoechoic mass lesions in the cervical stroma (Figure 11a). MRI is the most reliable modality to confirm the diagnosis, which shows low signal on all imaging sequences (Figure 11b).

The second part of this article will discuss imaging of endometriosis in the cervical canal and also cervical cancer. The importance of imaging in staging of cervical cancer will be presented.

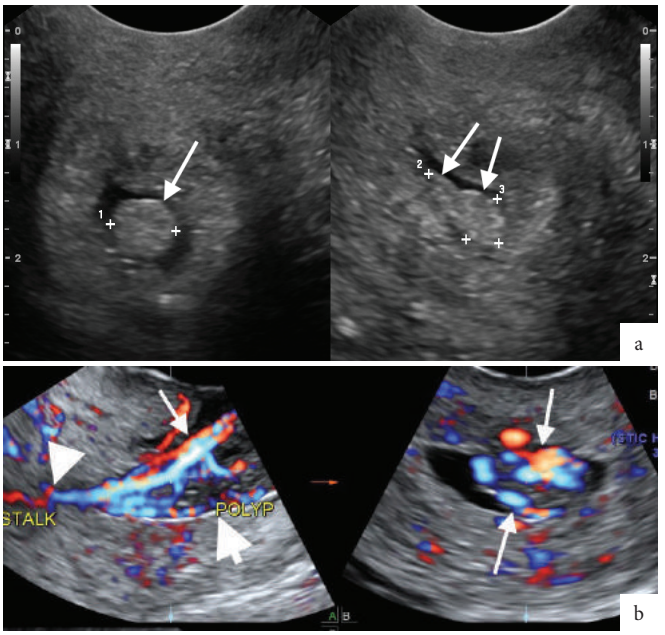


Figure 10a. Long and short axis US scans of the cervix showing an endocervical polyp (arrows). b. Long and short axis colour Doppler US scans showing an endocervical polyp (arrows) and the vascular pedicle (arrowhead).

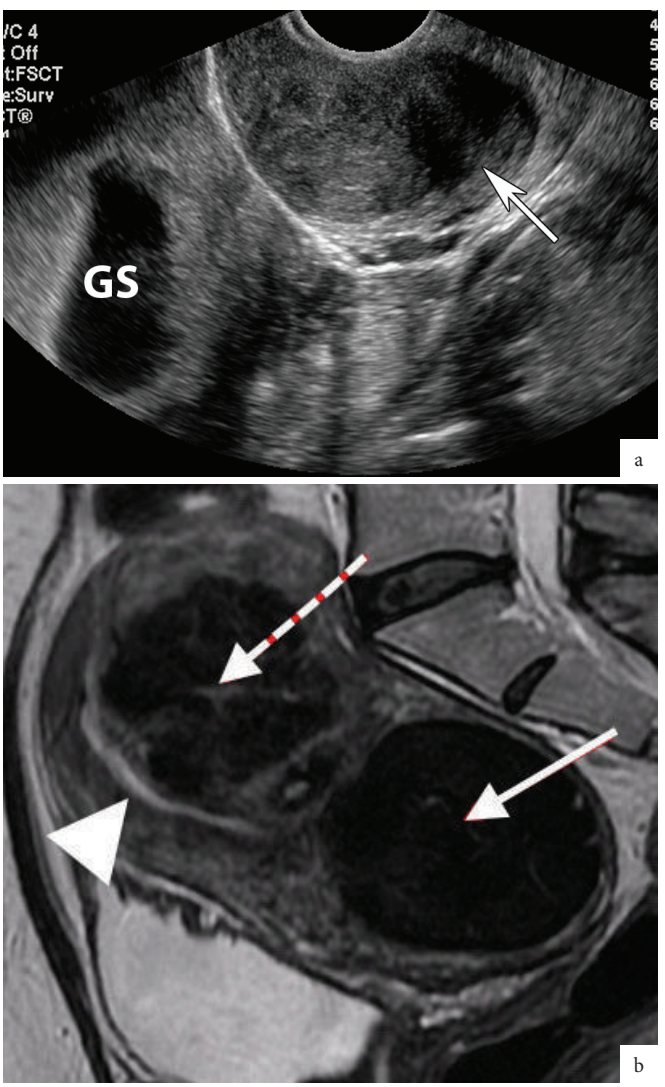


Figure 11a. Long axis US scan through the cervix showing a cervical fibroid appearing as a hypoechoic lesion (arrow) in the stromal layer. GS is an intrauterine gestational sac. b. Sagittal T2-weighted MRI scan showing a cervical fibroid (solid arrow) and a posterior body uterine fibroid (dashed arrow), the latter lying posterior to the endometrial cavity (arrowhead).

astellas

Prescribing Information
Presentation: Betmiga™ prolonged release tablets containing 25 mgor 50 mg mirabegron. **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adults (including the elderly): Recommended dose: 50 mg once daily. Children and adolescents: Should not be used. **Contraindications:** Hypersensitivity to active substance or any of the excipients. **Warnings and Precautions:** Should not be used in patients with end stage renal disease, severe hepatic impairment and severe uncontrolled hypertension. Not recommended in patients with severe renal impairment and moderate hepatic impairment concomitantly receiving strong CYP3A inhibitors. Dose adjustment to 25 mg is recommended in patients with moderate renal and mild hepatic impairment receiving strong CYP3A inhibitor concomitantly. Caution in patients with a known history of QT prolongation or in patients taking medicines known to prolong the QT interval. Not recommended during pregnancy and in women of childbearing potential not using contraception. Not recommended during breastfeeding. **Interactions:** Clinically relevant drug interactions between Betmiga™ and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected, except for inhibitory effect on the metabolism of CYP2D6 substrates. Betmiga™ is a moderate and time-dependant inhibitor of CYP2D6 and weak inhibitor of CYP3A. No dose adjustment needed when administered with CYP2D6 inhibitors or CYP2D6 poor metabolisers. Caution if co-administered with medicines with a narrow therapeutic index and significantly metabolised by CYP2D6. When initiating in combination with digoxin the lowest dose for digoxin should be prescribed and serum digoxin should be monitored. **Adverse Effects:** Urinary tract infection, tachycardia, palpitation, atrial fibrillation, blood pressure increase, leukocytoclastic vasculitis. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **Pack and Prices:** Country specific. **Legal Category:** POM. Product Licence Number: Betmiga™ 25 mg EU/1/12/809/003; Betmiga™ 50 mg EU/1/12/809/010. **Date of Preparation:** November 2012 **Further information available from:** Astellas Pharma Europe B.V. P.O. Box 344, 2300 AH Leiden, The Netherlands. Betmiga™ is a Registered Trademark. For full prescribing information please refer to the Summary of Product Characteristics. 20140312-UR-BTMA-08

Adverse events should be reported. Report adverse events to E.J. Busuttil Ltd. Tel: +356 21 44 7184