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THESYNAPSE

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Volume 15, 2016 Issue 05

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A maintenance bronchodilator treatment for patients with COPD who are breathless

ANORO™ ELLIPTA™

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. All rights reserved. Anoro® Ellipta® was developed in collaboration with Theravance, Inc.

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):

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/

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

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

"WEALTH SHALL REACH EVERYONE"

Or so was declared by the Hon. Minister of Finance Prof. Edward Scicluna during the speech relating to the Malta Budget 2017. For this editorial, we shall place it within the context of another well-known quote, attributed to Publius Vergilius Maro, commonly known as Virgil, one of the greatest Roman poets... "the greatest wealth is health"…

First of all, it should be kept in mind that the proposed expenditure for health in 2017 is set to be €517 million, representing 13% of the total budget. The following is a summary of the budget proposals for 2017:

- A project relating to a hospital specialising in the treatment of mothers and children is set to kick-start.
- Additional anti-diabetic medicines will be introduced in the government formulary. Furthermore, all patients suffering from Diabetes Mellitus Type 1 will now benefit from up to four blood glucose test strips per day, irrespective of age [as per DH Circular 442/2016 issued on 2 November]. An unspecified amount of glucose sticks will also be given for free to Type 2 diabetes patients.
- Diabetic patients who have the schedule V card [yellow card] will benefit from free dental care, subsidies on reading glasses and free access to antibiotics. This would address the abrupt removal of such benefits from diabetic patients by the previous administration.
- A reform in the schedule II card [pink card] medicinal entitlement is also being proposed.
- A public consultation will be carried out on the feasibility of workers using their sick leave to care for their sick children [this was actually a 2013 electoral pledge of the current administration but to date, this has not been implemented].
- Special medical paid leave over and above statutory sick leave will be introduced for employees diagnosed with cancer and undergoing treatment. In addition, Prof. Edward Scicluna stated that more anti-cancer medicines will be added to the government formulary.
- A regional hub offering primary health services is planned at the former Pace Grasso ground in Paola [this was also pledged in the Malta Budget 2016].
- A plan on how to employ a public-private partnership [PPP] model for the upgrading of Mount Carmel Hospital and the building of a new hospital for acute psychiatric care will be launched next year.

It goes without saying… if the government talks the talk and walks the walk, this would translate into a positive budget.

However, at this stage it is also important to note the unprecedented drive by the government to develop PPPs, also within the health sector through Projects Malta [www.projectsmalta.com]. Although PPPs within the health sector have been initially floated by the Nationalist party through the devolvement of surgical operations to the private sector and provision of beds to the elderly, the current administration has further expanded such PPPs to also include foreign participation and investment in the running of state hospitals [as well as in the provision of education pertaining to medicine]. More specifically, I am referring to the PPP relatin to Karen Grech Hospital, St Luke's Hospital and Gozo General Hospital between the Maltese government and Vitalis Global Healthcare [VGH]. The concession of these three hospitals to VGH is for 30 years and under the agreement reached earlier on this year, the government will buy a number of beds to be used by the public healthcare service from VGH. It has been reported that this will cost the government at least €55 million annually for medical services that are currently offered through the national health service.

As I said before, we are breaking new grounds. If indeed this and similar PPPs actually pay off, it will give a new meaning to "Wealth shall reach everyone". However, at this stage, only time will tell…

Ian Ellul

Cover: On 3 May 1783 the foundation stone for St Julian Hospital was laid in Victoria, Gozo. This hospital accommodated 50 patients and received unmarried pregnant mothers. It also provided foundling facilities. It ceased to function in 1864, becoming the Gozo Seminary in 1866. The Gozo Seminary is currently celebrating its 150th anniversary.

Photo Credit: Dr Ian Ellul

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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

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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

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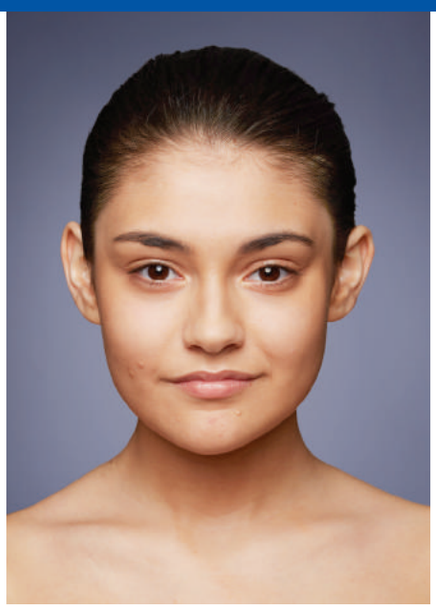
ISSUE GUIDE

TheSynapse

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



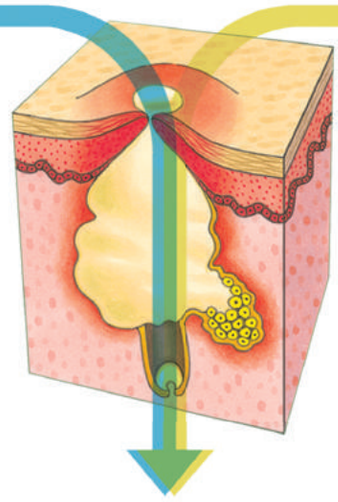
DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

- Keratolytic[2]
- 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

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 SPC, WHICH IS AVAILABLE FROM: GSK (MALTA) LIMITED (TEL: 21238131)

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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

For more information
www.hcp.gsk.com.mt/products/list/duac.html

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

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

HEALTHY, WEALTHY AND WISE

MAURICE CAUCHI

This trio of desiderata is no less valid today than when we were children, but the recipe for success, summarised as 'early to bed, early to rise', appears to be too simplistic in a complex world we live in today.

And yet, if you ask a hundred people, particularly those of a certain age, when they have started to realise that they are not indestructible any more, what is the most valuable thing in life, the majority would choose health as the most urgent priority.

Compared to most countries in the world, Malta is a healthy nation. We are also a happy-go-lucky nation where it seems that some things go reasonably well more through luck than through wise management.

Surveys have shown that Maltese consider themselves some of the happiest in the world. In a scale that ranked happiness in countries around the world, Malta is listed as the 30th out of 157 countries, beating countries like France, Italy, Cyprus, Japan, etc.[1] This index was built up from different components, namely: GDP per capita, social support, healthy life expectancy, freedom to make life choices, degree of generosity, perception of corruption, etc. So this is not just a subjective judgement of happiness, but is based on a number of socially-related factors. One factor which was not emphasized in this report is the efficiency of the health profession in producing this very acceptable state of affairs.

A more subjective Gallup survey consisted of interviews with people in 155 countries to obtain a 'life evaluation' score which varied on a scale from 1 to 10. Questions were asked relating to their experiences on the day previous to the interview and enquired about whether they felt well-rested, respected, free of pain, and intellectually challenged. On this scale also, subjective as it is, Malta ranked in the top quarter (at 38th position).[2]

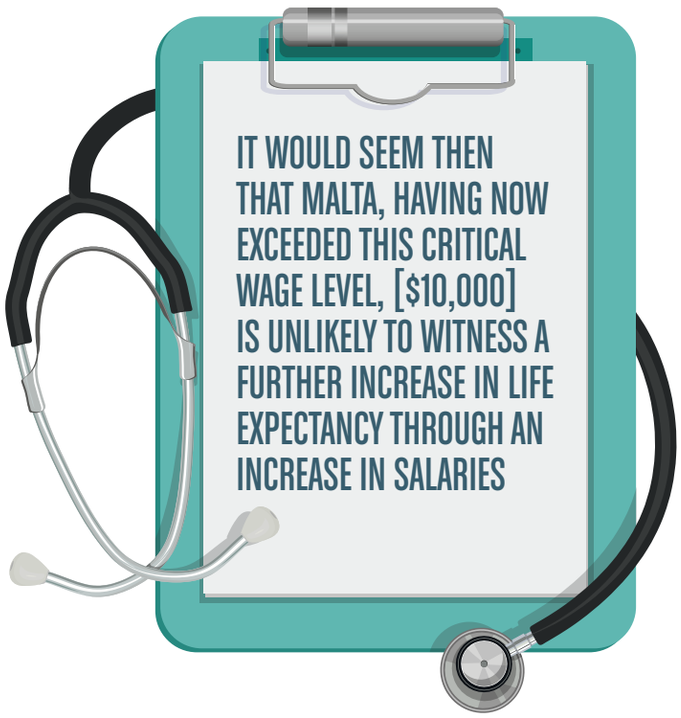
One important issue that comes out of the above study is that while 40% of Maltese were considered as 'thriving', nearly half of the population were classed as 'struggling', and 12% as actually 'suffering'.

Looking at any collection of data around the world, it becomes obvious that poor nations are also unhealthy nations. Not only are infectious diseases still the scourge of these nations, their short life is a constant battle for survival. The most obvious manifestation of poverty can now be seen as an explosion of people making the hazardous, often fatal rush to leave their country of origin and seek a home elsewhere, where the standard of living is higher and the future appears brighter.

Compared to the post-war period, when poverty was rife and the Maltese also had to leave these shores for pressing economic reasons, Malta has made gigantic economic progress. The standard of living is generally very good. The average salary has soared, from just over 10,000 euro in 2001 to over 17,000 euro in 2016,[3] a staggering 4% p.a.

In a recent publication *The Health Gap*[4], Sir Michael Marmot, former President of the British Medical Association, emphasized the point that while poverty and ill-health are causally related, there is, however, a level of wealth above which additional increments are unlikely to have a significant effect. He analysed the effect of income on life expectancy, and while confirming that those countries with the lowest incomes also have the lowest life-expectancies, he concluded that "above a national income of $10,000, there is little relation between income and life expectancy". In fact, he points out, that while the income is widely different in US compared to Cuba, there is little difference in life expectancy in US and Cuba. It would seem then that Malta, having now exceeded this critical wage level, is unlikely to witness a further increase in life expectancy through an increase in salaries.

[A RECENT STUDY FOUND THAT] WHILE 40% OF MALTESE WERE CONSIDERED AS 'THRIVING', NEARLY HALF OF THE POPULATION WERE CLASSED AS 'STRUGGLING', AND 12% AS ACTUALLY 'SUFFERING'.



The major point made by Marmot in this publication is the emphasis he made on issues impacting on health which are well beyond what a medical education equips us to deal with, issues with are rarely dealt with in medical textbooks or medical journals.

These factors relate to what he calls 'the social gradient in health'. While there have been great advances in the provision of medical facilities, including standards of hospital and medical practice in general, there is still quite an enormous variation within any one particular country between outcomes for those at the top of the social scale compared to those at the bottom. This differential is often the effect of social determinants of health which seem to be present in all 'developed' countries including Malta.

Life expectancy, for instance, is very much socially determined and varies significantly within a nation. Marmot gives as an example the fact that in the UK, for instance, if one takes the underground train ('Tube') from Westminster in central London, where better-off people are to be found, and move eastwards to the deprived areas of East London, life expectancy drops a year with every train stop!

Doctors and health practitioners in general deal with individuals to the best of their ability. They fix body ailments as best they can, and serve also as a repository of knowledge which they pass on to their patients and clients. They do not, in general feel obliged to delve deeply into the causation of disease, leaving this to public health professionals and researchers.

...IF ONE TAKES THE UNDERGROUND TRAIN ('TUBE') FROM WESTMINSTER IN CENTRAL LONDON, WHERE BETTER-OFF PEOPLE ARE TO BE FOUND, AND MOVE EASTWARDS TO THE DEPRIVED AREAS OF EAST LONDON, LIFE EXPECTANCY DROPS A YEAR WITH EVERY TRAIN STOP!

One major cause of ill-health which has not perhaps been given sufficient importance, but which now has taken centre stage, is the role of social inequality in perpetrating ill health amongst the community. There is no doubt that an unequal society, that is, one where there is a major differential between the well-off and those at the bottom of the social scale, leads invariably to a differential between the health of its citizens. While the western world is considered to be a rich and healthy world, there are invariably sections of the population where citizens are hit hard and health is at a nadir. Take for instance the US, a country which spends more on health than any other nation on earth, there is still a considerable proportion of citizens who have a markedly reduced life expectancy, and reduced access to health care, compared to much more 'equal' societies like Norway or Sweden.

Malta, a small country which is now actually doing well economically, one would have thought, qualifies as an equal society, with equal access to facilities and little differential between rich and poor. However, there is no doubt that here also we find pockets of want, and whole families at risk of poverty and ill-health.

The economist Lawrence Zammit claims that while the 'middle class' has increased significantly in size in Malta over the past 25 years, in recent years in Malta, we still find that up to 15.4% are at risk-of-poverty level.[5]

Moreover, certain localities in Malta are distinctly at a social disadvantage compared to the average. One objective yardstick is the distribution of social benefits by local area. A recent article published in *The Times* lists localities with the highest number of single parents in receipt of children allowance.[6] This report states that as of 2016 there were nearly 11,000 persons receiving such an allowance. St Paul's Bay and Birkirkara (the most populous localities in Malta) were at the top of the list. While females constituted the majority of these persons, about one-fifth of these single parents were males.

Social issues have been shown to play a very significant part in ensuring the creation and perpetuation of health issues. The general practitioner in particular, working at the coalface, is often considered to be the ideal person to detect the causes of ill-health. This option is, however, coming more and more under threat as a result of the fluidity of relationships between patient and doctor. The one-to-one relationship which used to be de rigueur in the past has been eroded, and with it the ability to diagnose familial, social, and other background factors which lead to disease in certain at-risk individuals and families.

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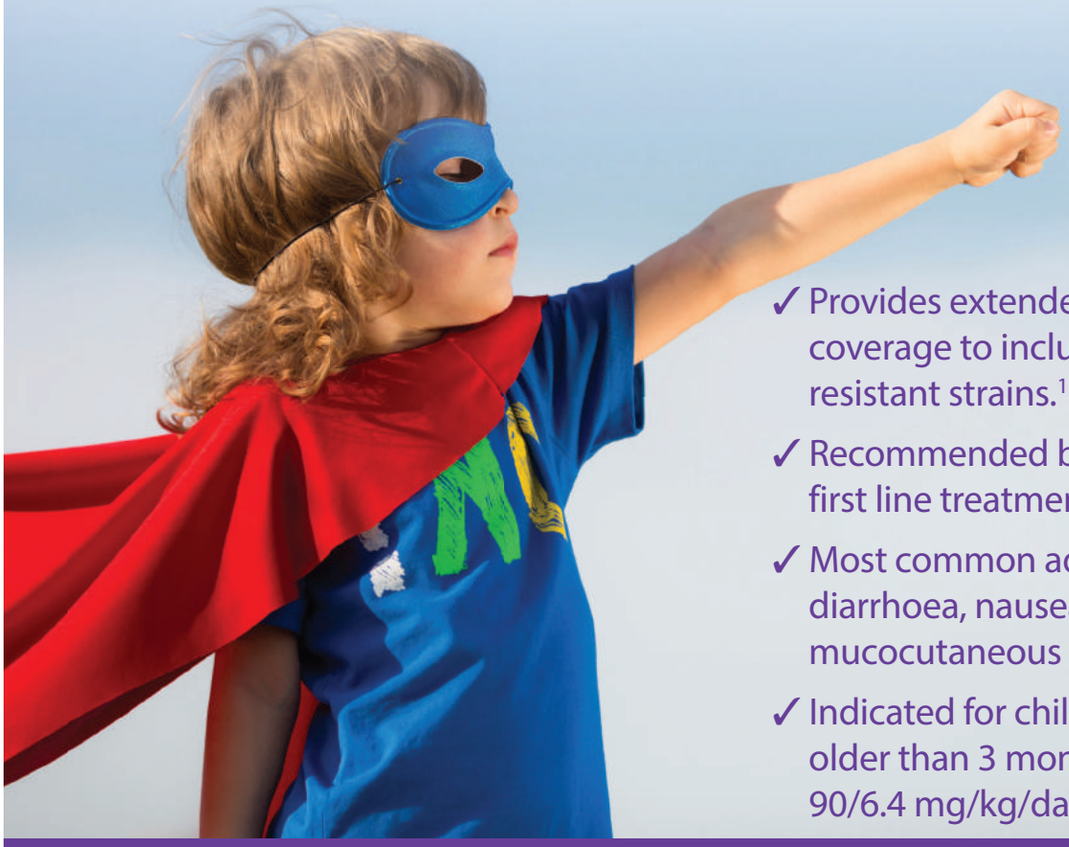
Augmentin® ES

600 mg/42.9 mg/5 ml

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]

Spreading infectious energy!

Mini Abridged Prescribing Information: *Please refer to the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATIONS:** Supplied in 100 ml glass bottle with a dosing spoon. **INDICATIONS:** 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 of 90/6.4 mg/kg/day in two divided doses. **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. Augmentin ES contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). *Refer to the SPC 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. **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 the SPC for full list of undesirable effects.* **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** May 2016 **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 m edication 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

References:

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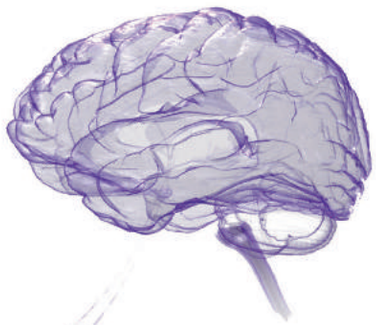
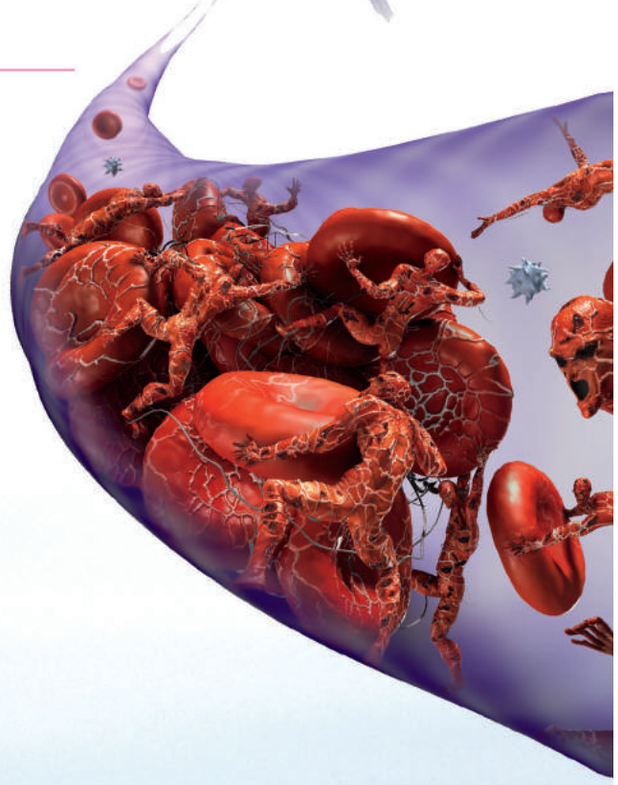
Prepared: November 2016 Job No: MLT_GIB/AES/0001/15(3)

For more information and dosing instructions:
www.hcp.gsk.com.mt/products/list/augmentin.html

One-Tablet, Once-Daily Xarelto®
for Stroke Prevention in AF[1]



Stroke devastates. Xarelto protects



Simplifying protection with no coagulation monitoring[1]

PROVEN EFFICACY

Highly effective, oral Factor Xa inhibitor[a,1,2]

PROVEN SAFETY

Adding protection by reducing ICH and fatal bleeds[b,1,2]

For further information, please visit
ThrombosisAdviser.com and Xarelto.com

ORAL, Direct Factor Xa Inhibition

Xarelto® rivaroxaban

Simple Protection for More Patients

AF=atrial fibrillation; ICH=intracranial haemorrhage.

Xarelto is not recommended for patients with prosthetic heart valves.

[a]Per-protocol, on-treatment analysis. Event rate: Xarelto (1.7%/yr) vs warfarin (2.2%/yr), $P<0.001$ for non-inferiority.

[b]Fewer intracranial haemorrhage events: Xarelto (0.5%/yr) vs warfarin (0.7%/yr), $P=0.019$. Fewer fatal bleeding events: Xarelto (0.2%/yr) vs warfarin (0.5%/yr), $P=0.003$.

Patients on Xarelto had significant increases in the following major bleeding events: a ≥2 g/dL fall in haemoglobin (2.8%/yr vs 2.3%/yr, $P=0.019$) and transfusions (1.7%/yr vs 1.3%/yr, $P=0.044$).

Mucosal bleeding events were seen more frequently with Xarelto compared with warfarin.

Bayer Pharma AG
Xarelto 15 mg / 20 mg film-coated tablets
(Refer to full SmPC before prescribing.)
▼This medicinal product is subject to additional monitoring. **Composition:** *Active ingredient:* 15 mg / 20 mg rivaroxaban. *Excipients:* Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172). **Indications:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Special populations: Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; active clinically significant bleeding; lesion or condition if considered a significant risk for major bleeding; concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy and breast feeding. **Warnings and Precautions:** Clinical surveillance in line with anticoagulation practice is recommended throughout treatment. Xarelto should be discontinued if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. *Not recommended:* in patients with severe renal impairment (creatinine clearance <15 ml/min); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with increased bleeding risk; in patients receiving concomitant treatment with strong CYP3A4 inducers unless the patient is closely observed for signs and symptoms of thrombosis; not recommended due to lack of data: in patients below 18 years of age, in patients concomitantly treated with dronedarone, in patients with prosthetic heart valves, in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Use with caution: in conditions with increased risk of haemorrhage; in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) or with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed. Specific dose recommendations apply for patients with moderate to severe renal impairment, in case of DVT/PE-patients only if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT/PE. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations. Xarelto contains lactose. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous and subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common in women* < 55 years treated for DVT, PE or prevention of recurrence), renal impairment, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Uncommon:* thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic function abnormal, urticaria, haemarthrosis, feeling unwell, increases in: bilirubin, blood alkaline phosphatase, LDH, lipase, amylase, GGT. *Rare:* jaundice, muscle haemorrhage, localised oedema, bilirubin conjugated increased, vascular pseudoaneurysm. *Frequency not known:* compartment syndrome or (acute) renal failure secondary to a bleeding. *Post-marketing observations (frequency not assessable):* angioedema and allergic oedema, cholestasis and hepatitis (incl. hepatocellular injury), thrombocytopenia. **Classification for supply:** Medicinal product subject to medical prescription. **Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany
Version: EU/4
Healthcare Professionals are asked to report any suspected adverse reactions as follows:
Report forms can be downloaded from http://medicinesauthority.gov.mt/adrportal and sent by post or email to;
P: ADR reporting/ Sir Temi Zammit Buildings, Malta Life Sciences Park, San GwannSGN 3000, Malta **E:** postlicensing.medicinesauthority@gov.mt
or **E:** pv@alfredgera.com

L.MT.GM XAR.2016.14

OPTIMIZING ANTICOAGULANT THERAPY IN NON-VALVULAR ATRIAL FIBRILLATION

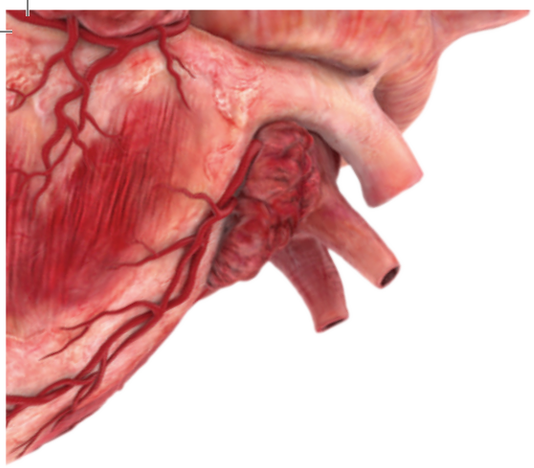
ANDREW CASSAR

The prevalence of atrial fibrillation (AF) is estimated to be around 3% of the population above 20 years of age, and increases with age, hypertension, cardiovascular disease, diabetes and obesity. Besides a 1.5- to 2-fold increase in mortality in people suffering from AF, they also have an increase in morbidity from heart failure and stroke. In fact, 20-30% of all ischaemic strokes are thought to be secondary to AF. The CHA_2DS_2-VASc score is a useful tool to quantify the yearly risk of stroke. One should note that the risk of stroke is independent of whether the AF is paroxysmal, persistent or permanent.[1]

Guidelines published by the European Society of Cardiology[2] (ESC) give a class I A indication for the prescription of oral anticoagulants (OACs) to males with a CHA_2DS_2-VASc score ≥ 2 and females with a score ≥ 3. One should also consider giving OACs to males with a score of 1 and females with a score of 2 (IIa B indication). No anticoagulants should be given to males or females with no additional risk factors, and anti-platelet monotherapy is not recommended whatever the stroke risk. A careful analysis of the patient's bleeding risk should be carried out before prescribing these drugs. Naturally, OACs should be avoided in patients with active bleeding, and concomitant antiplatelets should only be prescribed if indication is strong.

Vitamin K antagonists (VKAs) such as warfarin have been used for many years to reduce the risk of stroke and mortality in patients with AF. VKAs are limited by their narrow therapeutic interval, with patients needing frequent monitoring and dose adjustments. They are only effective in stroke prevention when delivered with adequate time in therapeutic range (TTR). In the last few years Non-Vitamin K Oral Anticoagulants (NOACs) have made an appearance on the market. All NOACs (the Direct Thrombin Inhibitor Dabigatran, and the Factor Xa inhibitors Rivaroxaban, Apixiban, and Edoxaban) have the distinctive advantage over VKAs of having a predictable effect, and therefore no need for monitoring. Treatment doses are well-defined; and all are given as a twice-daily dose, except for Rivaroxaban, which is given as a once-daily dose. All four NOACs were given regulatory approval after each of them had been compared to dose-adjusted Warfarin in large randomised trials and were proved to be, at least, non-inferior to Warfarin in the prevention of stroke or embolism. Comparison between NOACs based on these trials is difficult as the populations studied were different; notably the mean $CHADS_2$ score was 2.1 for dabigatran (RE-LY trail[3]) and apixiban (ARISTOTLE trial[4]) while it was 3.5 for Rivaroxaban (ROCKET-AF trial[5]).

The recently updated ESC guidelines recommend NOACs to be prescribed instead of VKAs when this is feasible (figure 1). Unfortunately NOACs are not yet available on the Maltese National Health Service, but patients might be willing to buy these drugs for their convenience and better safety profile. There are circumstances where one may actively suggest that a patient switches from Warfarin to NOACs. These include: Patients who have had a stroke or a bleed while on Warfarin, patients with labile INRs, and patients with low TTR. Patient with mechanical heart valves or mitral stenosis should be on VKAs and NOT given NOACs. In cases where a patient



IT IS STILL WORRYING THAT [ACCORDING TO THE GARFIELD-AF REGISTRY]SLIGHTLY MORE THAN 25% OF PATIENTS WITH CHA2DS2-VASC SCORE ≥ 2 WERE NOT ON ANY ANTICOAGULANTS

Table 1. Summary of ESC 2016 anticoagulation guidelines for stroke prevention in non-valvular AF.

Recommendations	Class	Level
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a **NOAC is recommended in preference to a Vitamin K antagonist.**	I	A
AF patients already on treatment with a vitamin K antagonist may be considered for **NOAC treatment if TTR is not well controlled** despite good adherence, **or if preferred by patient** without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A

with AF is unable to tolerate anti-coagulation, percutaneous closure of the left atrial appendage might be considered.

According to recently published data from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF)[6] - an ongoing, prospective, observational, worldwide study of adults with recently diagnosed non-valvular AF from 1215 sites in 35 countries - uptake of NOACs has increased steadily over the last few years. This has resulted in a greater proportion of patients being on guideline-recommended therapy. However, it is still worrying that slightly more than 25% of patients with CHA_2DS_2-VASc score ≥ 2 were not on any anticoagulants.

Unfortunately, the author is not aware of any data on rates of anti-coagulation of AF patients in Malta. The setting up of a local AF registry would be an important tool to enable the health authorities to reduce the number of strokes in our country by ensuring adequate anti-coagulation of patients. It is strongly encouraged that all doctors recommend anti-coagulation, preferably with a NOAC, to all AF patients with one risk factor or more and no contra-indications.

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Augmentin® SR

1000 mg/62,5 mg

Amoxicillin/Clavulanic Acid

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 the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin SR. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATIONS:** Supplied in 28 tablet packs. **INDICATIONS:** 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 is 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. Augmentin SR contains 29.3 mg (1.3 mmol) of sodium per tablet. *Refer to the SPC 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 the SPC for full list of undesirable effects.* **AUTHORISATION NUMBER:** AA 1051/00102. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** May 2016. **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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Prepared: November 2016 Job No: MLT_GIB/AES/0002/15(3)

For more information and dosing instructions:
www.hcp.gsk.com.mt/products/list/augmentin.html

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 GZR 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/

References
1. Wildhaber, J *et al. Pediatr. Pulmonol* 2012; 47:346–357.
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

C STANDS FOR CANCER

MARIO SALIBA

Last year I read the editorial of *The Synapse Journal*, '**C stands for Cancer … Colleagues … Compassion**.'[1] This has motivated me to narrate my personal experience …

All doctors from time to time deal with harrowing stories of patients being struck with serious illness and cancer. Like many, I had coped with these experiences during my thirty three years as a family doctor by adopting a firm belief that it could never happen to me.

Unsurprising then, my sense of shock when, a few months ago late in the afternoon I received the results of my second prostate biopsy. If I am totally honest, I knew what was coming as I have a strong family history of prostate cancer. Initially the MRI scan had left me with some hope as the report read 'a suspicious lesion' and a follow-up was suggested. So I had clung to the slim hope it was just a big scare. I was still in denial that it can happen to me and hoped that although it could happen it was not now but at some later stage in life.

The best thing I did was that I stopped acting as a doctor and I submitted myself to the full guidance of my consultant and started to act as a patient. Honestly, it was impossible to completely block out my professional background. I would worry about a suspicious lesion on the MRI, the first normal biopsy and make (incorrect) assumptions about the significance of a normal blood test result, as the PSA was never more than 3.1 (monitored over a period of five years). I still remembered lecturers and clinicians telling us during our semiotics tutorials many years ago that disease manifests itself differently in different people even though we label it with the same name. I continued with my consultations or rather discussions, as I should say that my consultant always involved me in resolving the issue until a full diagnosis was made. So with a bit more persistance from my end and gentle patience from my consultant, a repeat guided biopsy was made and left me with no doubt.

Despite years of training in clinical communication skills, I now know how it is that patients only recall the first sentence when bad news is broken. "I have the results of your biopsy and I am afraid it is not good news", was what I heard my consultant say on the mobile. I had been diagnosed with prostate cancer. The surgeon reassured me that it was not bad as it was at an

THE EFFICIENCY AND PROFESSIONALISM WITH WHICH MY CASE WAS HANDLED LIVED UP TO HIGH STANDARDS

early stage. He encouraged me to talk to the pathologist to get it explained and he made me an appointment to discuss it face-to-face with him and bring over my wife. Despite all the reassurances I got from both, the rest of the call passed in a blur. In that moment it felt like my whole identity had been turned on its head. I was no longer a doctor, I was a cancer patient with all the fears and questions that anyone faced with that diagnosis experiences: how will I cope? Who will look after the family? What will happen with work? Will my wife manage? Will I die? I imagined the worst scenario possible. Then the doctor in me took over again. I started looking up the medical literature about the management of early prostate cancer. On one occasion, I stumbled across a paper in a clinical journal about complications from the treatment of prostate cancer and *made the mistake of reading it.* The verdict from the literature review was not clear and I knew that I had three choices, active surveillance, and radical prostatectomy or localised brachytherapy. I had already made up my mind and my view was respected by the consultant but he acted very professionally and suggested that he presents my case in a multi-disciplinary meeting which is an indispensable aid to communication between different specialities. He also reminded me of all the possible side effects and complications from the treatments. Perhaps I was hoping for reassurance, but the stark facts in front of me had the opposite effect. I learned my lesson, and avoided reading articles about my condition and over-analysing my blood tests or scan results. From then on, I wanted nothing more than to hand over that responsibility to the experts.

Patient choice is an important consideration in the type of treatment given provided this is available locally but if there is a specialised treatment that is indicated the team of consultants will recommend that you are sent abroad. Although I knew what the options for me were, more important still was having confidence in the expertise of those around me to make the right decisions on my behalf. I consider myself fortunate in that I knew what was happening and what path I will eventually follow. How much harder it must be for most patients who must put blind faith in those around them!

In my case the multi-disciplinary team of consultants recommended robotic surgery and this was my decision to follow from the first days of thinking about treatment. Unfortunately this specialised type of keyhole surgery is not available in Malta. So they sent all my results to a specialised hospital in London where they carry out this type of operation. A few weeks later we received confirmation that they agreed and they were booking me for surgery in the UK.

During all this process, however, by necessity my anonymity could not be maintained in its entirety. All my results were on the IT hospital system. My case was discussed at multi-disciplinary meetings and I sometimes wondered if the colleagues I walked past knew about my diagnosis. I continue to avoid being the patient until the last week I left for treatment. In England the environment was completely different. I was just a patient. Although the doctors knew that I was myself a doctor all other staff didn't know and I just let them do their job as professionals. I should say that seven out of ten of the hospital staff were foreigners from different European countries, Africa or South America. The common thing between them is that they respect the dignity of the patient and they all maintain the same high standards of care.

In a time of bewildering uncertainty, the knowledge that the NHS machinery would kick into action and be there for you is hugely reassuring. Within a few weeks I was laying inside the Isotope scanner unit for a whole body CT scan, getting further tests to stage my cancer. The efficiency and professionalism with which my case was handled lived up to high standards. We hear so much about the failings of the UK's NHS in the tabloids that the many small daily achievements when things go as planned often pass by unnoticed. Our health system is one of the best in the world. It is complimented by special agreements with different specialised hospitals so that the most up-to-date treaments are provided to all Maltese and Gozitan patients free of charge at the point of use.

Everyone who strives to provide gold-standard treatment within the NHS knows that what matters is that patients receive the most modern treatment in a timely fashion. But as a patient I also learned that the small things matter too. Like a friendly word from the nurse looking after you during your stay in the hospital after surgery, or the secretary you call to check on your next appointment, or even like clear signposting indicating the out-patients or urology department. All of these things help to smooth the patient's journey in a way that is difficult to quantify.

I have completed my treatment now and have made the testing transition back to work. I am able to reflect on the lessons I have learned in the last year or so and the unexpected insights that I will take forward with me as a doctor. As I look towards the future as a doctor I hope to put to good use the lessons I have learned as a patient. I end this narration with a quotation included in the related editorial of *The Synapse Journal*[1] which I mentioned in the opening paragraph … *True compassion means not only feeling another's pain but also being moved to help relieve it* (Daniel Goleman).

REFERENCE

1. C stands for Cancer, Colleagues, Compassion [Editorial]. *The Synapse Medical Magazine* 2015; 14(2):3.

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:

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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

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BOOK REVIEW

MORGUE: A LIFE IN DEATH

Forensic science is booming. TV dramas, books and movies have made morgues cool. Complex technology and intricate research can take curdled blood, bone shards, and flakes of skin and turn them into justice. And Dr Vincent Di Maio is one of the lions of forensic science in his own right. In this clear, gritty, and enthralling narrative, Di Maio himself guides us into the inner sanctum, through the cases that have made him famous, from the exhumation of assassin Lee Harvey Oswald and the racially charged shooting of Florida teen Trayvon Martin, to the unmasking of a serial baby-killer and the mysterious death of troubled genius Vincent van Gogh. Along the way, one of the country's most methodical and intuitive criminal pathologists will dissect himself, maintaining a nearly continuous flow of suspenseful stories, revealing anecdotes, and enough macabre insider details to rivet the most fervent crime fans.

About the Author

Dr Vincent Di Maio is an American pathologist and an internationally renowned expert on gunshot wounds. Now a private consultant who's performed more than 9,000 autopsies, he's played pivotal roles in some of the most provocative trials and death investigations of the past 40 years. He is editor-in-chief of *The American Journal of Forensic Medicine and Pathology.*

Ron Franscell is the bestselling crime author.

By: Vincent DiMaio & Ron Franscell
Published By: St. Martin's Press
Pages: 288
Published: May 2016

Source: *amazon.com*

JOKE

Curiosity Matters

This Indian boy goes to his mother one day with a puzzled look.

"Mom, why is my bigger brother named Thunderstorm?" She told him, "Because he was conceived during a mighty storm."

Then he asked, "Why is my sister named Cornflower?" She replied, "Well, your father and I were in a cornfield when we made her."

"And why is my other sister called Moonchild?" "Because we were watching the moon landing while she was conceived."

Thoughtfully, Mother paused and asked her son, "Tell me, Broken Rubber, why are you so curious?"

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- **Significant improvements in Quality of Life** vs enalapril, as measured by reduced deterioration of heart failure symptoms and physical limitations ($P=0.001$)[7§]

When you see symptoms, IT'S TIME FOR ENTRESTO[5]

Entresto®
sacubitril/valsartan

ARR=absolute risk reduction; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; RAAS=renin-angiotensin-aldosterone system.

*The complementary cardiovascular benefits of ENTRESTO in patients with HFrEF are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitril and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan.

†Based on 2016 ESC HF Guidelines and 2016 ACC/AHA/HFSA Guideline Update.

‡Primary end point.

§Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

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 in 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. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. 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/1/15/1058/006-007. 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. 2016-MT-ENT-16-JUN-2016

References: 1. Fala L. Entresto (sacubitril/valsartan): first-in-class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. *Am Health Drug Benefits*. 2015;8(6):330-334. **2.** Volpe M, Camovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci*. 2016;130(2):57-77. **3.** Ponikowski P, Voors A, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200. **4.** Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America [published online ahead of print May 20, 2016]. *Circulation*. doi:10.1161/CIR.0000000000000435. **5.** ENTRESTO Core Data Sheet, version 1.1. Novartis Pharmaceuticals; August 2015. **6.** McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure. *Eur J Heart Fail*. 2013;15(9):1062-1073. **7.** McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

NOVARTIS

A MEDITERRANEAN INFECTION RE-VISITED

MEDICAL ANECDOTES - short accounts of interesting cases, some medical disasters, involving pathology and clinical practice, from the recollection of ***Prof. Albert Cilia-Vincenti***

This is 1970 and Professor JV Zammit-Maempel, just before going on holiday for three weeks, sees a 22-year-old in a domiciliary consultation, with fever, constipation and a vague skin rash, and refers him to his ward at St Luke's Hospital with a diagnosis of "?typhoid" and with instructions to start chloramphenicol intravenously. Chloramphenicol in those days was a very popular antibiotic – inexpensive and with the widest spectrum. It did however carry the rare risk of bone marrow damage and fatal aplastic anaemia. I do, in fact, remember carrying an autopsy on a young English woman who was given chloramphenicol in Spain, developing aplastic anaemia and subsequently transferred to London's St George's Hospital where she died, and where the case was presented at the physicians' grand round.

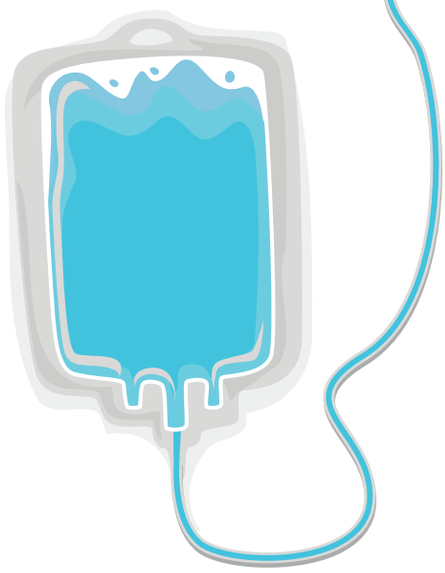
Professor Zammit-Maempel maintained that no aplastic anaemia complication had ever been reported with chloramphenicol delivered intravenously, instead of orally, so a ten-day course of i.v. chloramphenicol was his favourite antibiotic regime. Back to the young man with the "?typhoid" diagnosis; I was the house officer, so we started the patient on the i.v. chloramphenicol, and Zammit-Maempel left on holiday without seeing this patient in the ward. A young senior registrar, recently returned from UK with his MRCP (not common in those days), had joined our firm and was now in charge of the ward.

The patient's pyrexia soon resolved but after a few days it returned. Tests for typhoid were negative. The senior registrar discovered this young man had had a "hole-in-the heart" operation in London when he was a kid, and therefore suspected subacute bacterial endocarditis (SBE). Chloramphenicol was stopped and penicillin started. Fever resolved but returned again after a few days. Leishmaniasis was excluded when a bone marrow aspirate was reported negative. In desperation, a course of tetracycline was instituted, but again, fever went down and returned after a few days. By this time the patient was emaciated and almost moribund, and Zammit-Maempel was due to return from holiday.

As soon as Zammit-Maempel returned, we got him to see this young man who had now been administered religious last rites. The senior registrar reminded Prof that he had referred this patient with a "?typhoid" diagnosis, and which had not been confirmed, SBE was suspected and adequate penicillin course given, Leishmaniasis had been excluded, and we were dealing with a rapidly deteriorating case of pyrexia of unknown origin. Zammit-Maempel leafed through the notes and declared he must be suffering from Leishmaniasis. The senior registrar protested that it had already been investigated and excluded. However, Zammit-Maempel insisted that he was suffering from Leishmaniasis – emphasising the two peaks every 24 hours on temperature chart, neutropenia and enlarged spleen. He reasoned that neutropenia and SBE don't go together. Repeat bone marrow aspirate proved Zammit-Maempel right and i.v. antimony was started.

Fast forward to mid-1980s, I am a consultant surgical pathologist in Winchester, southern England. Dr Anthony Galea-Debono and Mr Anthony Zammit are looking after a young haemophiliac with AIDS in Malta who's got rectal bleeding from "?kaposi sarcoma" bowel lesions. One lesion is biopsied and referred to us. Microscopically the lesion consists of macrophages containing probable Donovan bodies. I sent some slides to Professor Sebastian Lucas in London (a histopathologist with a special interest in exotic infections) to confirm that it was Leishmaniasis, which he does. In the late 1980s, writing a chapter in "Advances in Histopathology", Lucas uses this Maltese case (with due credits) to illustrate the emerging picture of Leishmaniasis complicating AIDS in the Mediterranean.

Fast forward yet again to mid-1990s and I have returned to a consultant pathologist's post in Malta. It is Christmas time and a young bachelor friend of ours returns from work overseas for the festive season. He is, however, ill-looking and says he's pyrexic. A family doctor refers him to St Luke's Hospital where a medical senior registrar suspects he's very immune compromised, excludes Leishmaniasis with a negative bone marrow aspirate, and asks him whether he would take an HIV test. The patient is septicaemic and Professor CP Mallia warns his parents that he's in danger of dying. Patient refuses to have an HIV test, saying that he would commit suicide if it were positive. I reassure him that there is now treatment, if positive. He improves with i.v. antibiotics and goes back overseas. A few days later he phones saying he's feverish and weak again. I insist he gets to the nearest hospital immediately. There he goes into total system failure, almost dies in intensive care, he's found to be HIV-positive, and Leishmaniasis is now diagnosed on a bone marrow aspirate. After a slow recovery, including renal dialysis for a couple of months, he returns to health after lengthy treatment for Leishmaniasis. He of course is still on HIV drugs, but is now in his early fifties, healthy and fit, and has held a number of very senior positions overseas.



Addendum: the update on Cholesterol & Statins (Issue 4) did not clarify that the C-reactive protein (CRP) test referred to in cardiology circles is the high-sensitivity (hsCRP) variety. The normal CRP has little better sensitivity for inflammation than an ESR and is useless for atherosclerosis risk assessment. HsCRP is available in the profiles of some local private laboratories but apparently still unavailable at Mater Dei Hospital.

DIABETES

JESSICA ZARB

MPSA

November is diabetes awareness month. WHO estimates that 8.5% of the global population suffers from diabetes.[1] Diabetes is a chronic metabolic disease characterized by hyperglycemia resulting from abnormalities in insulin secretion, insulin action or insulin sensitivity. This chronic disease is associated with long term impairment, dysfunction and deterioration of different organs.

There are three types of diabetes:

Type 1 Diabetes in which the individual's immune system destroys insulin-producing cells in the pancreas. This leads to a reduction in the capability of the body to produce insulin, requiring daily administration of insulin. The most common delivery devices are syringes, pens or pumps. Client education is vital and should encompass comprehensive information on caring for and using insulin, prevention, recognition and treatment of hypoglycaemia, adjustments of food intake and self-monitoring of blood glucose. Multiple daily injections is the most common method to attempt to mimick pancreatic insulin secretion.

Type 2 Diabetes results from a progressive increase in resistance of the body to insulin. This type is most common in the middle-aged and elderly, however it is becoming more common in younger populations. Medications such as metformin and sulfonylureas are normally prescribed. However, insulin therapy is given to patients with severe diabetes. In the past insulin was used as a last resort, nevertheless nowadays insulin is prescribed earlier because of its benefits.

The last type of diabetes is ***Gestational Diabetes*** which is the onset of diabetes during pregnancy in an individual with no previous symptoms. This type is caused by insulin defiance during pregnancy and may lead to Type 2 Diabetes.

During the diabetes awareness month, MPSA launches a health campaign to further draw the attention of the public to possible symptoms.

REFERENCE

1. http://www.who.int/mediacentre/factsheets/fs312/en/

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

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

COPD

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:

- 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 100/25mcg compared with fluticasone furoate 100mcg 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/RESP/0004/16 Date of preparation: Feb 2016

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Theravance

WRITE A SCIENTIFIC PAPER – MALTESE COURSE IN LONDON

PROF. VICTOR GRECH
M.D., PH.D. (LOND), PH.D. (MALTA), F.R.C.P.C.H, F.R.C.P.(UK), D.C.H.
Consultant Paediatrician (Cardiol), MDH
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Editor-in-Chief, *Images Paediatr Cardiol*
& Editor, *Malta Medical Journal*

In the sciences, actually doing research is only part of the picture. This is because publishing papers on one's research is vital. If the outcomes and results of research studies remain unpublished, whether positive or negative, the resources that went into that research will be wasted as someone else may well redo the identical research work. Access to extant research and building on this research is thus vital for the progress of science.

Furthermore, in most countries, research funding is apportioned by the number and importance of the grant applicant's publications. Participation at congresses with oral or poster presentations is also invaluable. But the gold standard remains the original paper written and published in a reputable journal.

Write a Scientific Paper is a three day intensive course with formal lectures and interactive sessions. This is an international and unique course that has been successfully held in Malta in 2010, 2011, 2012, 2013 and 2016. Each iteration has led to fine tuning of the contents via feedback from successive attendees.

The course is now being held for the first time in London. This event attempts to facilitate all aspects of paper writing. The course is delivered by highly experienced researchers. The purpose is to impart the lecturers' collective experience to the delegates in this crucial aspect of career progress. This event is endorsed by the Royal College of Paediatrics & Child Health.

Faculty to date: Prof. Victor Grech, Prof. Charles Savona-Ventura, Prof. Josanne Vassallo, Prof. Jane Somerville and Dr Alessandro Giardini.

The event will be held on 30 January - 1 February, 2017 at the Royal College of Paediatrics & Child Health in London, and has been awarded 18 EU and internationally recognised EACCME accreditation points.

WRITE A SCIENTIFIC PAPER WASP

Website: www.ithams.com/wasp/
Facebook: www.facebook.com/events/929892130477166/
This event has been organised by The Institute of Technology, Humanities, the Arts, Medicine and Science and The Malta Institute for Medical Education.

TOP WEB READS THESYNAPSE.net

THE DECLINE AND FALL OF THE SACRA INFERMERIA

Dr Giovanni Bonello
Former European Court of Human Rights Judge

NEGLIGENCE AND CIVIL LIABILITY IN THE MEDICAL PROFESSION

Dr Sonia Vancell
B.Pharm.(Hons.) M.A. (Eur. Stud.) LLD

Dr Franco Vassallo
LLD

Courtesy of TCV MAMO Advocates

THE PHARMACIST'S JEKYLL AND HYDE BEHAVIOUR: IS ABSOLUTE UNITY POSSIBLE? REFLECTIONS ON THE *MOVIMENT VUĊI GHALL-ISPIŻJARA*

Mr Charles Micallef
B.Pharm.(Hons.) M.Sc.
PA & PH (Staff)

BREXIT, THE PHARMA INDUSTRY & MALTA'S AVAILABILITY OF MEDICINES

Dr Ian Ellul
PhD (Paed.)

MEETING THE EDITOR

MARIKA AZZOPARDI

An interview with Dr Ian Ellul - editor of *The Synapse Medical Journal* as well as researcher in paediatric medicine.

TS: WHAT IS YOUR BACKGROUND?

"I am a pharmacist by profession. I believe that this vocation initially sprouted at home, since my mother is a nurse and my sister is a pharmacist (although, truth be told, in hindsight, I wonder whether it would have been a wiser option to follow the steps of other cousins, since I would have ended up as deputy prime minister or judge!). Following graduation as a pharmacist, I furthered my studies by taking up doctorate studies on a part-time level. I considered a PhD with the Faculty of Medicine and Surgery to be a better option to any other 3-year part-time Masters-equivalent course. The study period lasted nine years and successfully ended two years ago."

TS: WHAT WAS YOUR PHD RESEARCH AREA?

"The studies were conducted within the department of Paediatrics, under the supervision of Prof. Victor Grech. The main research related to off-label and unlicensed use of paediatric medicine in the community setting in Malta and Gozo. This research was requested by the European Commission. So my studies effectively bridged this knowledge gap for Malta. In view of the fact that I started my studies a couple of months before the scholarship scheme was introduced by the previous government, I ended up paying every last cent of the research. At this stage I also need to thank Prof. Simon Attard-Montalto, Dr Paul Vassallo-Agius, Dr Herbert Lenicker and Prof. Liberato Camilleri [brilliant statistician] for their invaluable help."

TS: WHAT WERE YOUR MAIN FINDINGS?

"We found that almost one in two prescriptions were being prescribed in an off-label or unlicensed manner. It is however, important to bear in mind that such prescribing [within the principle of therapeutic freedom] does not mean that these medicines were being prescribed in an unsafe manner. Rather, the two main contributing factors were a lack of appropriately licensed paediatric medicines and lack of harmonisation between the product literatures of medicines containing the same composition of active ingredients. In fact, against this backdrop, the main concern by participants related to medico-legal issues.

Ian Ellul, Student Representative delivering the Graduand's speech during the Graduation Ceremony, November 2014

The highest incidence of off-label or unlicensed prescribing was found in the 1 month – 2 years age range. More paediatricians, rather than family doctors, prescribed in an off-label or unlicensed manner for age. Conversely, more family doctors, rather than paediatricians, prescribed in an off-label manner for dose.

During the course of the research I was privileged to be invited at conferences in various European cities as speaker, including Genoa, Rome, Marseille, Brussels, Liege, Warsaw, Dublin, Prague and London. I was also lucky to receive one of five travel scholarships awarded by the Drug Information Association. Our research was also published in various peer-reviewed European and US journals. The last publication is *Can Registration Procedures of pharmaceuticals inadvertently Contribute to Off-Label Prescribing in Children?,* published earlier this year in the official journal of the Drug Information Association."

TS: YOUR WORK HAS NOT BEEN SOLELY ACADEMIC. IN FACT FOR SOMEBODY SO INTERESTED IN ACADEMIA, YOU HAVE REALLY MOVED AROUND. CAN YOU EXPLAIN MORE ABOUT YOUR JOURNEY WITHIN YOUR FIELD?

"I started as a director of pharmacy services with the St James Group. Afterwards I took a job at the Medicines Authority for eight years in the licensing directorate. During that time, I was appointed national coordinator for clinical trials. This involved setting up from scratch the framework for the regulation of clinical research in Malta; I personally transposed and translated

the relevant EU legislation. After that experience I became a partner in a private business. In the meantime I was also approached to be a second-line responsible person, as well as conduct local literature surveillance of adverse events, for a couple of pharmaceutical companies. In 2013 I was also asked to head the regulatory affairs office of a major institution, however I declined in view of my studies. Presently I work as technical evaluator at the Central Procurement and Supplies Unit, evaluating tenders relating to medicinal products, foods and medical devices within the Ministry of Health. Since 2004 I have been on the board of the Health Ethics Committee whose remit includes the evaluation of proposals for research being conducted in the health sector, including ethical and data protection aspects. Most surprisingly, our appointment expired in August 2014 and the new committee has never been appointed. Maybe the reason is that we do not get paid, so there aren't a lot of people interested in replacing us!

Recently, I was also privileged to be invited by the British Medical Journal to be a peer reviewer."

TS: WHAT DO YOU DO IN YOUR FREE TIME?

"For quite a number of years I was involved on a voluntary basis within the Kummissjoni Djoċesana Żgħażagħ. This is where I met my wife. So the Kummissjoni holds a special place in my heart. Another key initiative I was involved in was the setting up of a youth centre in Luqa in 2003. I remember that at the time I was nursing a broken ankle and it dawned on me that young people in Luqa did not have any social meeting place. I started the ball rolling together with a couple of good friends, also from Luqa. I am proud to say that the group is still going strong."

TS: SO VOLUNTARY WORK WAS IMPORTANT ON SEVERAL COUNTS. YOU MENTIONED MEETING YOUR WIFE ...

"Yes we have been married for two and a half years and are the proud parents of a 1 year old girl … fatherhood is a remarkable thing …"

TS: AND OF COURSE YOU ARE THE MANAGING EDITOR OF THE SYNAPSE MEDICAL JOURNAL.

"I remember when I started to be involved with the production of the journal, over 11 years ago, when the publication was a two-colour eight-pager. Over the years it has definitely evolved. Today it carries between 28 - 32 pages in four-colour (full colour). The *Synapse Journal* is basically unrivalled within the Maltese medical field since we print a yearly average of 180 pages over 6 issues which are printed, then mailed, to practically each and every doctor, pharmacist and dentist in Malta. Each print run is 3500 copies.

We try to collaborate closely with various key stakeholders, namely the Malta Medical Students Association, Malta Pharmaceutical Students Association, Malta Association of Dental Students, German Maltese Medical Society, Health Promotion Department, University of Malta, Department of Health Information, Chamber of Pharmacy and many others besides. Recently we also had the pleasure of including articles by various lawyers including Dr Yana Micallef Stafrace [**Percentage disability reports in the medical field**], Drs Sonia Vancell & Franco Vassallo [**Negligence and Civil Liability in the Medical Profession**] and Judge Giovanni Bonello [**The Decline and Fall of the Sacra Infermeria**]. Apart from articles, each issue includes an interview [like this one] with a key professional which is a great way to getting to know peers. We also place a great effort in featuring fronts which are somewhat related to medicine, be it medicinal plants, paintings by medics or pharmacists or historical medical buildings.

Sixty-seventy hours of my time goes into each publication. Responsibilities include the development, acquisition and management of content, as well as overseeing the overall layout of articles. The core tasks include copywriting and content writing. Considering that each issue is posted to 3,500 subscribers, including several foreigners, it must be carefully and meticulously compiled."

SUGGESTED READ

Ellul IC, Grech V, Attard-Montalto S. **Can registration procedures of pharmaceuticals inadvertently contribute to off-label prescribing in children?** - *Ther. Innov. Regul. Sci.* 2016;50(6): 808-816. Available from: http://dij.sagepub.com/content/50/6/808

Background: In Malta, off-label prescribing of medicines in children stands at 45%, mainly because of failure by prescribers to follow the dosing recommendations in the product literature. In addition, registration procedures of pharmaceuticals may inadvertently contribute to this high incidence of off-label prescribing.

Methods: A literature review was conducted to identify regulatory provisions relating to the registration of medicines in Malta that could give rise to off-label use. Furthermore, the product literature of the 2 classes of medicines most commonly prescribed in children, antibiotics and respiratory medicines, were reviewed. This was done in order to gauge whether the different registration routes implemented in Malta to market these medicines could give rise to off-label use.

Results: The national registration procedure relating to Article 126a of Directive 2001/83/EC and, to a lesser extent, line extensions, parallel importation, and the provision detailed in Article 11 of Directive 2001/83/EC were found to lead to discrepancies and potentially misleading inclusions in the product literature. These, in turn, may well contribute to off-label use of medicines in children.

Conclusions: Off-label prescribing does not necessarily mean that efficacy and safety data are unavailable. Variances in the product literature of medicines having the same active ingredients but imported from different countries may cause divergent prescribing practices, leading to inadvertent off-label use. The various stakeholders, including member states such as Malta, should devise strategies to harmonize the most recent labeling information in order to support the safe and effective use of pediatric medicines, thereby decreasing off-label use.

GALVUS and EUCREAS
COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

GALVUS is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

EUCREAS is the combination of a DPP-4 inhibitor, GALVUS, and metformin[2]

Galvus®
PRESENTATION: Each tablet contains 50 mg of Vildagliptin INDICATIONS: For the treatment of type 2 diabetes mellitus in adults: As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with: metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years). The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinediones have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients. Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class III treated with Vildagliptin is still limited and results are inconclusive. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. Use of Vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). Monotherapy: Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Combination with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Uncommon: headache, asthenia, hypoglycaemia. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulence. Frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. **LEGAL CATEGORY:** POM **PACK SIZES:** 7, 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 003. **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 +356 21222872. 2015-MT- GAL-18-DEC-2015

Eucreas®
PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with maximum and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice-daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination therapy with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFTs should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10): Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 30, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park, Camberley, GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–003, EU/1/07/425/035-039. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from: Novartis Pharma Services Inc. Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872 2015-MT-EUC-18-DEC-2015

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NOVARTIS

1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics

THE MAMMOGRAPHICALLY DENSE BREAST:

STRATEGIES IN BREAST CANCER IMAGING

PIERRE VASSALLO

We have known for some time that a dense breast on mammography presents diagnostic problems in the detection of breast cancer. It has also been suggested that women with dense breasts are at a higher risk for developing breast cancer.

The aim of this article is to update the reader on current thoughts and data on the above issues and discusses the use of supplemental imaging in women with dense breasts, including digital breast tomosynthesis (DBT), whole-breast ultrasonography (WBUS), automated whole-breast US (ABUS), and gadolinium-enhanced breast magnetic resonance (MR) imaging.

Breast density refers to the visual characteristics of the breast on mammograms. Breasts containing a high proportion of parenchymal elements and ducts compared to background fatty tissue are considered dense, while those containing a higher proportion fatty tissue are considered non-dense or fatty in composition. In layman's terms, a dense breast has more "white" elements that may be patchy or confluent (Fig 1a), while a fatty or non-dense breast contains more "dark" elements (Fig 1b) on a mammogram.

Breast density does not correlate with firmness noted on clinical palpation. A firm breast may have a predominantly fatty composition, while a soft breast may have a dense composition on mammography.

Breast density has been classified into four groups: fatty breasts, scattered fibro-glandular elements, heterogeneously dense breasts and very (or homogeneously) dense breasts (Fig 2). There is significant variation in classification between different observers and even between repeat reviews by the same observer, particularly towards the middle of the scale, due to its non-quantitative nature. There have been attempts to quantify breast density on digital mammograms through software analysis with very limited success.

Data from the Breast Cancer Surveillance Consortium (BCSC) collected from registries around the United States show that on 934,098 normal screening mammograms

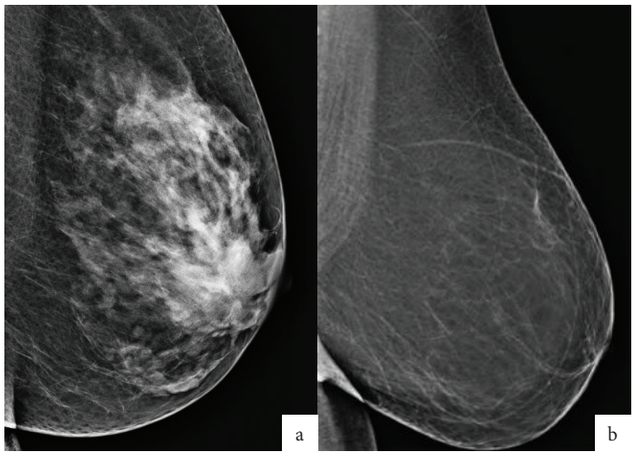

Figure 1. Mammograms showing a heterogeneously dense breast (a) compared to a fatty breast (b).

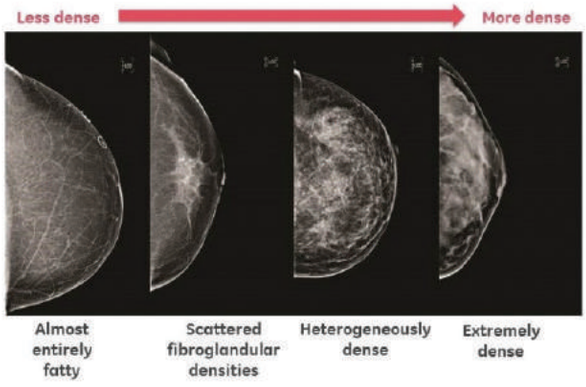

Figure 2. Grading of breast density on a mammogram.

obtained from 1994 to 2008, the distribution according to tissue density was as follows: 9.0% of breasts were fatty breasts, 44.1% were breasts with scattered areas of fibro glandular densities 38.3% were heterogeneously dense breasts, and 8.6% were extremely (or "homogeneously") dense breasts. In clinical practice, fatty breasts and those with scattered fibro glandular elements are referred to as **non-dense breasts**, while those that are heterogeneously or extremely dense are referred to as **dense breasts**.

Importantly, breast density diminishes with increasing patient age and body mass index. A decrease in blood oestrogen and progesterone levels as seen most notably at menopause, will

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result in a decrease in glandular and ductal components and a relative increase in fatty components in the breast. Weight-loss or gain will influence the fat content in the breast and will alter breast density (Fig 3).

Higher breast density may obscure a breast cancer during mammographic evaluation and result in later diagnosis when the cancer is more advanced. This observation has led to the introduction of legislative changes in several states in the USA that obliges the radiologist to notify the patient regarding her breast density and the possible need for supplemental imaging.

There is considerable evidence that breast cancers can be obscured by dense breast tissue. Past studies have used the concept of **interval cancers** to distinguish those cancers that appeared on mammograms obtained **within 1 year of the prior mammograms**. **Non-interval cancers** were those detected after a period **greater than 12 months from the previous mammograms**. It was found that in women with dense breasts, the proportion of interval cancers was significantly higher than in those with non-dense breasts. The incidence of non-interval cancers was higher in women with non-dense breast

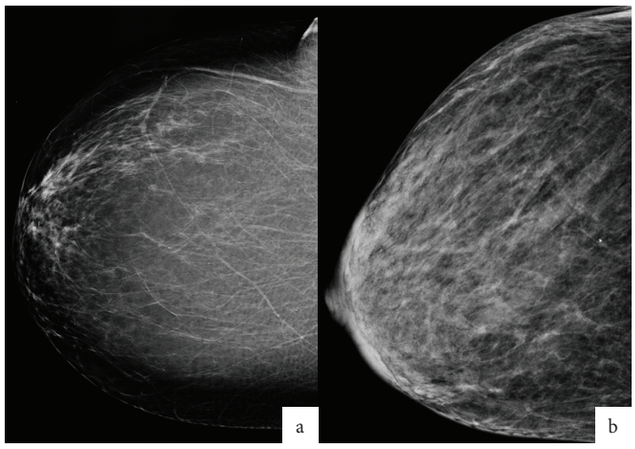

Figure 3. Mammograms of the same patient taken 2 years apart, (a) before and (b) after considerable weight loss.

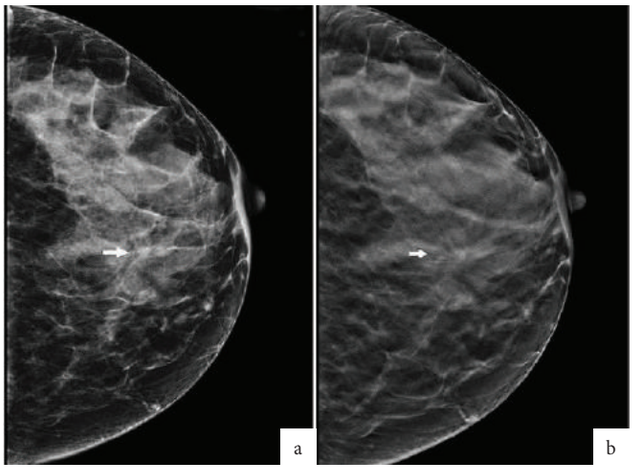

Figure 4. DR (a) vs CR (b) Mammograms: The same lesion (arrow) is more clearly depicted on the DR mammogram than on the CR mammogram.

HIGHER BREAST DENSITY MAY OBSCURE A BREAST CANCER DURING MAMMOGRAPHIC EVALUATION AND RESULT IN LATER DIAGNOSIS

that in those with dense breasts. This lead to the conclusion that very early signs of breast cancer may have been obscured by abundant parenchymal elements in dense breasts on the initial mammograms.

Other supporting evidence for the obscuring effect caused by dense parenchymal elements has been obtained through the use of supplemental investigations such as breast ultrasound (US), digital breast tomosynthesis (DBT) and breast MRI, which help detect cancers that are not visible in dense breasts. Numerous studies have evaluated the use of supplemental imaging to improve breast cancer detection, however significant differences in study design and patient selection criteria between these studies make it difficult to reach concrete conclusions.

A most significant improvement in the ability to evaluate the dense breast was seen with the introduction of Digital Mammography. The image quality provided by digital mammograms significantly improved visualisation of the dense breast compared to earlier film/screen mammograms. There are two types of digital mammograms: Computed Radiography (CR) Mammograms and Full Field Digital Mammograms (also known as DR Mammograms). **DR Mammograms have a much better image quality than CR Mammograms** (Fig 4). **FFDM is the gold standard for breast cancer screening today.**

A standard strategy used by most radiologists when faced with a mammogram showing dense breasts is to proceed to a breast ultrasound (or WBUS) to obtain a second view of those difficult-to-analyse areas on the mammogram. Breast ultrasound does not rely on tissue density to create an image, it relies on tissue and cell interfaces that act as acoustic reflectors. What is seen a dense on mammography is usually well penetrated by the ultrasound beam. Mammographically difficult areas in the breast are usually cleared with a breast ultrasound often performed in the same sitting (Fig 5) providing an efficient and effective mode of patient management.

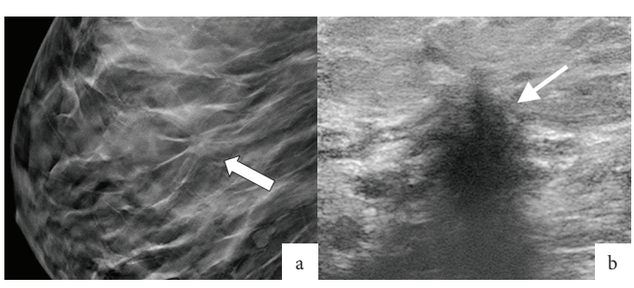

Figure 5. Suspected lesion (arrow) on mammogram (a) was clearly confirmed on breast ultrasound (b).

Breast ultrasound is widely available and inexpensive, but it is strongly both operator and technology dependent. The abundance of older ultrasound machines in many hospitals and radiology practices and the lack of trained expertise would significantly reduce its value for breast cancer detection. The approval of ABUS but the FDA (Food and Drug Administration, USA) in 2011, may take a step towards improving the situation. ABUS takes a mechanically-controlled scan through the whole breast and records a 3D image for review by the radiologist. The inherent advantage of free-hand breast ultrasound is that the examiner is able to rotate the probe to select the best plane of lesion visibility. This is not possible with ABUS. ABUS has not been approved for breast cancer screening.

DBT is a new technology based on DR Mammography, which obtains a series of images at different levels through the breast similar to the consecutive slices obtained with Computed Tomography (CT). Sometimes referred to as 3D mammography, it is not a 3D imaging method as the thickness of the slices obtained is too large to allow 3D reconstructions. DBT appears to be of value in the dense breast as it reduces lesion superimposition by dense parenchymal structure (Fig 6). However, DBT is used as an adjunct to standard DR mammograms with the consequence that there is a doubling of radiation exposure to the patient if DBT is performed in just one plane. DBT is therefore not recommended in this format as a screening method for breast cancer. It can be used to evaluate patients with abnormal mammograms or those with significant clinical suspicion. The possibility to create synthesised DR mammograms from DBT data would reduce the radiation exposure by avoiding initial DR Mammography and may in future lead DBT becoming a primary screening tool.

MR Imaging of the breast is the most sensitive test available for detecting breast cancer. It will depict more cancers that DR Mammography or Breast Ultrasound, but it also has a higher false positive rate, which would result in unnecessary breast biopsies. There are clear guidelines that recommend the use of breast MR imaging for screening women with a high risk for breast cancer. Whether it should also be used for intermediate or low risk women is as yet undecided. Breast MR imaging depends on morphological features and contrast enhancement characteristics to detect cancerous lesions in the breast (Fig 7). Long examination times, limited scanner availability, high cost and the need for intravenous injection of contrast material limit the use of MR imaging for breast cancer screening.

A further question relating to the dense breast is whether breast density in itself makes the patient more prone to breast cancer. This is a subject under constant debate. The higher volume of glandular and ductal elements in dense breasts, which are the tissues that give rise to breast cancer, may raise the patient's risk. There is some statistical evidence that breast density may influence a patient's risk to develop breast cancer, however other risk factors such as positive breast cancer gene testing, family and personal history and obesity and smoking play a greater role.

The dense breast poses a very frequent problem encountered in the breast cancer screening with mammography. The use of supplemental imaging, mainly breast ultrasound and MR imaging, significantly improves the accuracy of diagnostic assessment in the mammographically dense breast. Finally, correlation of clinical with imaging data is of great importance as clinical data may provide helpful guidance in those difficult areas in the dense breast.

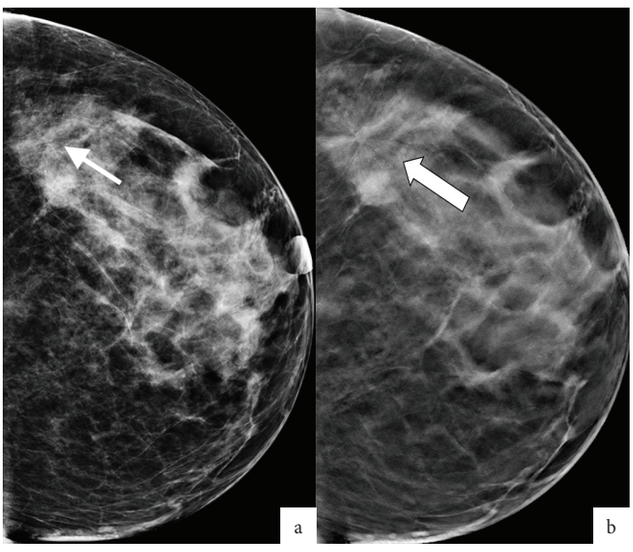

Figure 6. Subtle lesion (arrow) seen on DR mammogram (a) better seen on supplemental DBT (b).

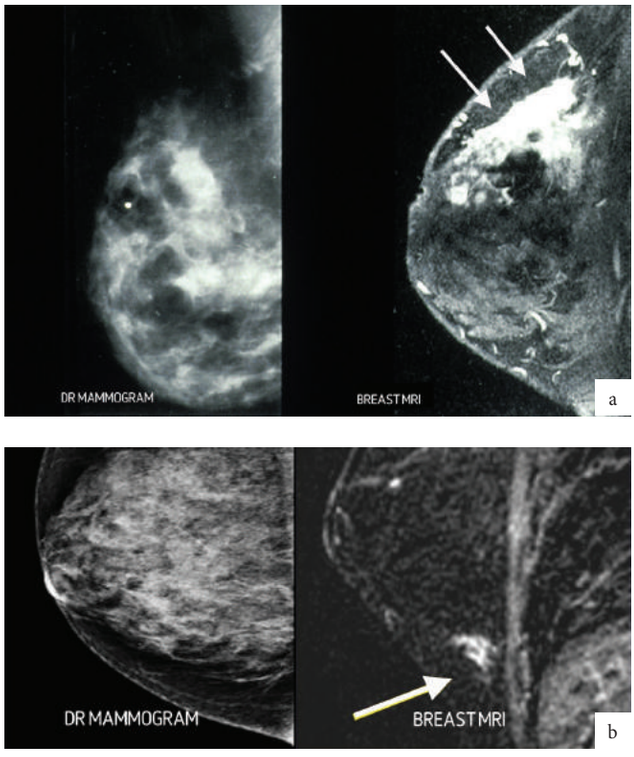

Figure 7. Two cases of cancer (a and b) obscured in dense breasts that were visible (arrows) on MR imaging.

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