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THE MEDICAL PROFESSIONALS' NETWORK

Metastatic melanoma: how do local treatment options compare with current standards of care? -

Interview with Oncologist Dr Nicholas Refalo

Volume 15, 2016 Issue 06

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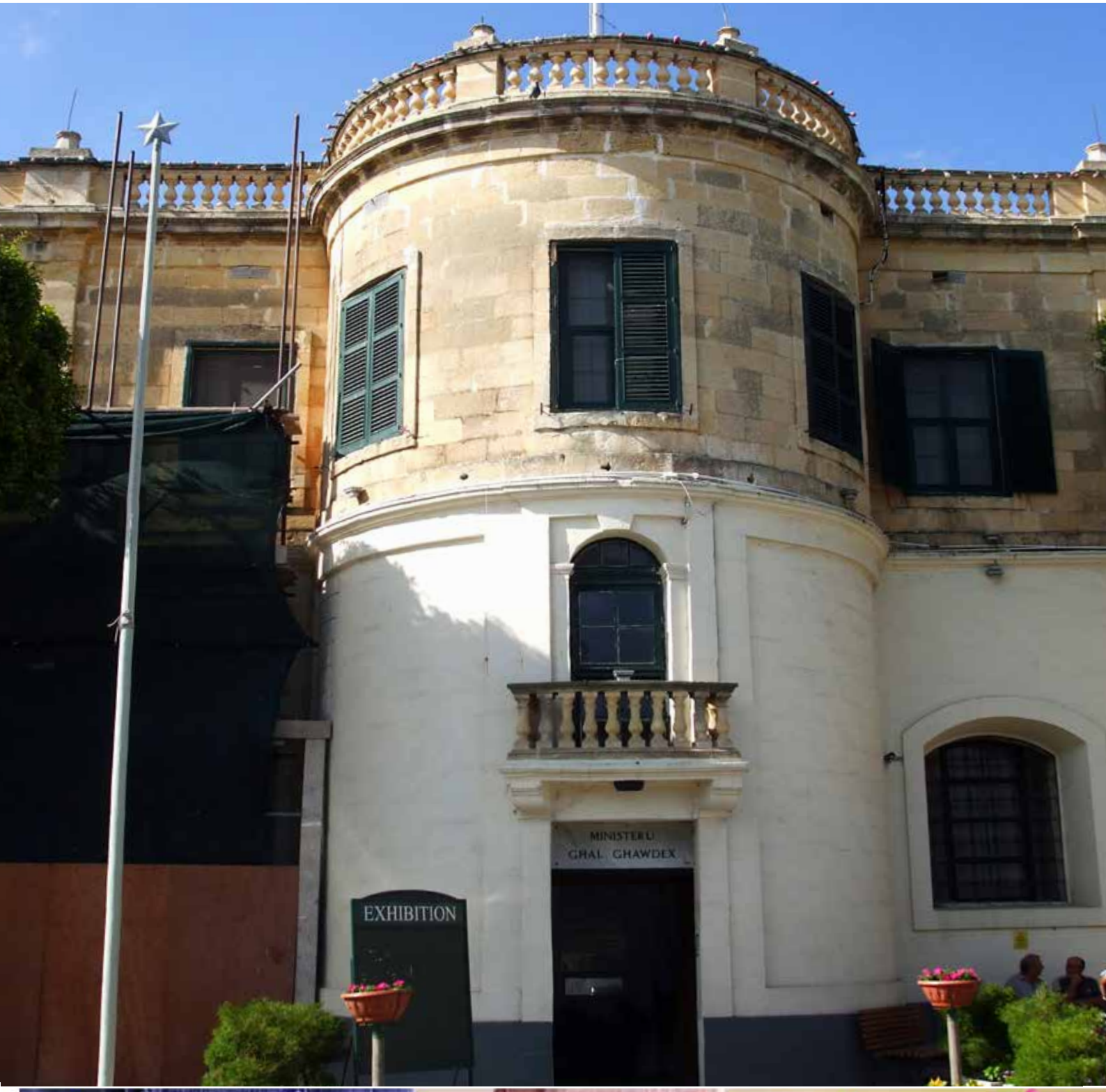

Actifed*

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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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

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

THOU SHALT NOT PRESCRIBE ANTIBIOTICS...

According to the report, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations,[1] it is estimated that at least 700,000 people succumb from microbial-resistant infections around the globe each year. It is indeed predicted that by 2050, antibiotic resistance will cost the world up to a staggering €88,000,000,000,000 as well as a reduction of 2% - 3.5% in global GDP. We are partly to blame for this, considering over-prescriptions, over-the-counter selling of antibiotics, as well as veterinary misuse. Interestingly, the Health at a Glance: Europe 2016,[2] published in November, reports that of all EU countries, Malta has the highest proportion of second-line antibiotic use [32%]. The EU27 average is 18%.

How can we tackle this problem, or at least part of it? Interestingly, Jason Doctor, director of health informatics at the University of Southern California's Schaeffer Center for Health Policy and Economics, has been carrying out experiments to see whether it is possible to [at least] reduce over-prescriptions.[3] He persuaded 248 physicians working in 47 primary care practices in Boston and Los Angeles to participate in a cluster randomized clinical trial. The interventions included:

1. Placing a poster in the examination room with the picture of the physician and signature showing a public commitment to not over-prescribe antibiotics;
2. Physicians had to explain their reasoning for the prescribed drugs;
3. Comparing physicians to other top-performing physicians within the cohort [those with the lowest inappropriate prescribing rates].

These interventions effectively reduced the number of antibiotic prescriptions. In fact, similar interventions are now being applied in health departments across the United States and even in the EU.

However, if one were to completely eliminate over-prescribing [and illicit over-the-counter use of antibiotics], this would not solve the problem relating to antimicrobial resistance. The reason for this is very simple … there is an even bigger market of antibiotics. In 1950, a group of US scientists found that adding antibiotics to animal feed increases the growth rate of livestock. Ever since, antibiotics have been pumped in animals, even though we are all aware of the fact that bacterial resistance passes from animals to humans. On many occasions, any bans on growth-promoting antibiotics have been circumvented by using different labeling. Furthermore, it is envisaged that countries such as China, Brazil and Russia, will double their use of antibiotics by 2030. This has spurred researchers to try to source novel antibiotics from different sources such as the algae-filled fur of a three-toed sloth in Panama [at least this country is not only the home of tax evaders], the saliva of Komodo dragons, blood of alligators, bacteria in British Columbia caves and on the ocean floor off the coast of Panama.

REFERENCE

1. Review on Antimicrobial Resistance. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance, London, United Kingdom. 2014.
2. OECD/EU. Health at a Glance: Europe 2016 – State of Health in the EU Cycle, OECD Publishing, Paris. 2016.
3. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. JAMA. 2016;315(6):562-70.

Cover: The Hospital of St. John the Baptist opened in Victoria Gozo, on 14 October 1729. The hospital changed its name to Victoria Hospital on the occasion of Queen Victoria Jubilee in 1887. In 1957 it reportedly had a bed compliment of 26 [medical], 40 [surgical], 12 [maternity], 6 [gynaecological] and 10 [pediatric] beds. It ceased to function in 1975. The hospital was re-utilized for other Government purposes including the Gozo Ministry.

Photo Credit: Dr Ian Ellul

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

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A maintenance bronchodilator treatment for patients with COPD who are breathless

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)

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

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

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

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ISSUE GUIDE

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HEARTFUL THANKS GOES TO ALL READERS, CONTRIBUTORS, REVIEWERS & SPONSORS WHO CONTRIBUTED TOWARDS OUR SUCCESS IN 2016.

WISHING YOU ALL A PROSPEROUS 2017.

AN OVERVIEW OF THE EPIDEMIOLOGY AND LOCAL HEALTH SERVICES OFFERED FOR COLORECTAL CANCER

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ABSTRACT

Colorectal cancer is the second most common cancer in Malta. On average, between 2012-2014, 259 persons have been diagnosed with colorectal cancer and 110 persons died each year. It is a disease of the Western world. The need to target colorectal cancer from prevention through physical exercise and healthy eating, to earlier diagnosis and treatment, through organised screening programmes and fast track referral systems and advanced treatment protocols is crucial to reduce incidence and improve survival.

INTRODUCTION

Colorectal cancer accounts for 9.7% of all cancers worldwide (excluding non-melanotic skin cancer). It is the second most common cancer in Europe and third most common cancer in the world.1 It is far more common in the Western world with age standardised incidence rates being highest in Europe and North America (Table 1) and lowest in Africa and Central America.[1]

Population	Numbers	Crude Rate	ASR (W)
World	1360602	19.3	17.2
Africa	41105	3.8	6.3
Central America	11601	7.2	8.0
South America	67464	16.8	15.7
Morthern America	158169	45.1	26.1
Asia	607182	14.3	13.7
Central and Eastern Europe	139856	47.6	26.6
Northern Europe	65162	65.0	30.4
Southers Europe	105009	66.7	31.1
Malta	268	63.9	31.9
Western Europe	137109	72.3	31.4

[+] *(age standardised rates using the world standard population)*

Table 1: Estimated incidence in specific world regions, both sexes, 20121

There is variation in the trends in incidence and mortality of colorectal cancer in different countries with three main patterns being observed:

- Increase in incidence and mortality is being seen in rapidly transitioning regions such as Eastern Europe, Asia and South America;
- Increase in incidence with a decrease in mortality is being seen in some European countries such as Denmark, Sweden, United Kingdom and Malta amongst others as well as Canada and Singapore;
- In countries such as the United States, Japan and other Western countries both incidence and mortality have stabilised or have even started to decline.[2]

Colorectal cancer is associated with a number of modifiable risk factors including diets rich in animal fat and protein, obesity and lack of physical activity, smoking and excessive alcohol consumption. Inherited conditions such as familial adenomatous polyposis (FAP) as well as a personal history of inflammatory bowel diseases[3] are associated with a high risk of developing colorectal cancer. The latter risk conditions account for only a small proportion of all colorectal cancer cases.

A reduction in colorectal cancer incidence and mortality is achievable through a number of measures which include primary prevention through improved nutrition and increased physical activity, and organised population-based cancer screening programmes. New and advanced treatments are also contributing towards improvements in the outcomes of colorectal cancer care. There are wide variations worldwide in the state of implementation of colorectal screening with countries such as the United States and Japan having organised screening programmes since the 1990s.[4] On the other hand, by 2008, only 19 out of the 27 EU countries had or were developing a screening programme.[5] By 2015, this implementation figure has gone up to 24 out of 28 EU countries.[4] However, to date there are still several countries worldwide with no organised screening programme in place despite having a high incidence and mortality from the disease.[4]

EPIDEMIOLOGY OF COLORECTAL CANCER IN MALTA

COLORECTAL CANCER INCIDENCE

Colorectal cancer is the second commonest cancer for Malta in both genders combined following breast cancer. On average, 146 males and 113 females (3 year average of 2012-2014) are diagnosed each year with colorectal cancer. The incidence of colorectal cancer increases with age (Figure 1) and age-specific incidence rates in males are much higher than those in females for most age groups.[6]

The standardised incidence rate of colorectal cancer in Malta has remained relatively stable in females (Figure 2) but seems to show a rising trend in males. Incidence rates in Malta in both males and females are lower than the EU average (Malta: M: 42.1, F: 35.2; EU-27 average: M: 59.0, F: 36.1 in 2012 per 100,000 pop (ESP).[7]

COLORECTAL CANCER MORTALITY

MORTALITY

On average there are 61 male deaths and 49 female deaths due to colorectal cancer each year (average of 2012-2014). Colorectal cancer is the second most common cause of cancer death in both sexes combined following lung cancer. Average age at death for both genders is 73 years (2012-2014). The age standardised mortality rate has remained relatively stable in males over the past years (Figure 3) but is showing a downward trend in females.6 Mortality rates in Malta in both males and females are slightly above the EU average (Malta: M: 23.9, F: 15.9; EU-27 average: M: 23.8, F: 14.2 in 2012 per 100,000 pop (ESP)).[7]

SURVIVAL

The one-year and 5-year relative survival for patients with invasive colon cancer who were diagnosed between the years 2000-2007 was 77.6 and 57.0 respectively in Europe.[8] Malta

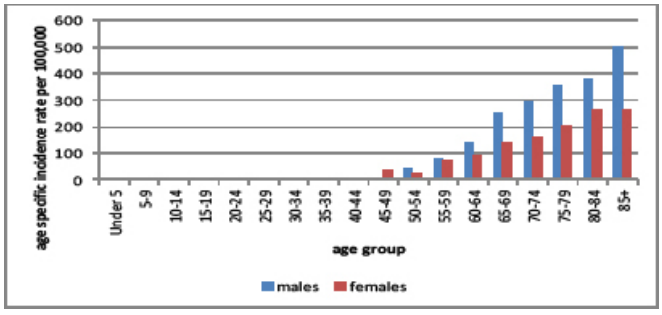


Figure 1. Yearly age-specific incidence rate for colorectal cancer (average of 2012-2014), by gender[6]

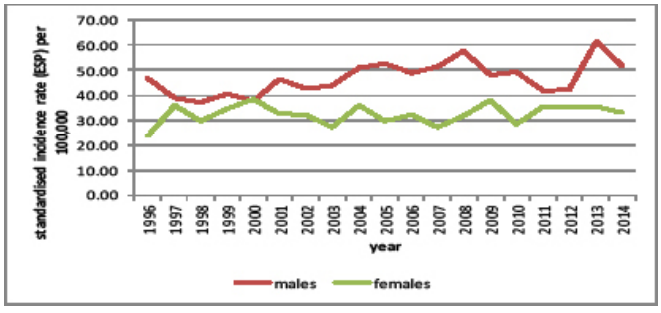
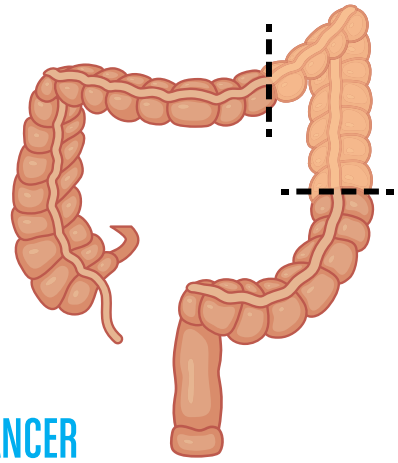


Figure 2. Trends in standardised incidence rate (European Standard Population) in males and females in Malta[6]

COLORECTAL CANCER IS THE SECOND COMMONEST CANCER FOR MALTA IN BOTH GENDERS COMBINED FOLLOWING BREAST CANCER



observed one of the highest increases in colon cancer 5-year relative survival from 53% for patients diagnosed between 1999-2001 to 61% in patients diagnosed with *colon* cancer in 2005-2007.[8] As presented in the tables below, one-year relative survival of patients with rectal cancer is higher than those with colon cancer in all regions. However, the same does not always apply for the 5-year relative survival. In Malta, between the periods 1999-2001 and 2005-2007, the 5-year relative survival for patients with *rectal* cancer fell from 60% to 50% (European average increased by 6 percentage points to 58%).[8]

SERVICES FOR THE MANAGEMENT OF PATIENTS WITH COLORECTAL CANCER IN MALTA

Prior to the introduction of the colorectal screening programme in Malta in November 2012, screening for colorectal cancer by faecal occult blood tests (FOBT) and other means was only performed on an opportunistic basis and activity rates were very low. Only 2.6% of persons aged between 50 and 74 years interviewed in the European Health Interview Survey carried out in 2008 reported as having had a FOBT in the previous two years.[9]

The National Colorectal Cancer Screening programme was launched in November 2012. During its first screening cycle, persons aged between 60-64 years were invited to undergo colorectal cancer screening. The colorectal cancer screening programme is now in its second cycle and persons aged 55 to 66 years are invited to undertake an iFOBT (immunochemical-faecal occult blood test) every 2 years. Clients that obtain a positive iFOBT result are referred for a colonoscopy. The aim is to eventually reach the age cohorts 50 to 74 years recommended in the EU Council Recommendation of 2003 on Cancer Screening.[10]

Apart from the screening route, patients can also enter the colorectal cancer care pathway from the symptomatic route. A number of measures are being planned and introduced to ensure that patients with suspicious signs and symptoms gain access to specialist care in hospital in the shortest time possible. One of these measures involves the introduction of a fast-track referral system. **A pilot system relating to the fast-track referral system for colorectal cancer was introduced in early 2016 whereby participating family physicians can complete an electronic referral form that has been specifically designed for this purpose.** A surgeon with a special interest in colorectal surgery vets these referrals. When the indication for a fast-track

A PILOT SYSTEM RELATING TO THE FAST-TRACK REFERRAL SYSTEM FOR COLORECTAL CANCER WAS INTRODUCED IN EARLY 2016 WHEREBY PARTICIPATING FAMILY PHYSICIANS CAN COMPLETE AN ELECTRONIC REFERRAL FORM THAT HAS BEEN SPECIFICALLY DESIGNED FOR THIS PURPOSE

referral is confirmed, the family physician is instructed on how best to prepare their patient and an expedited appointment for a colonoscopy is given.

Measures are also being planned to ensure continuity and seamless care for patients navigating the cancer pathway from diagnosis to palliative care and survivorship. The aims are to improve patients' experience and outcomes and also to assist patients during this challenging journey. These include the planned and incremental introduction of cancer care pathway navigators. These navigators will most often be nursing professionals and they will be appointed to act as care-coordinators for patients with various cancers. Navigators will be assigned to different groups of cancer patients so that they will be able to develop specific expertise in assisting patients with similar conditions.

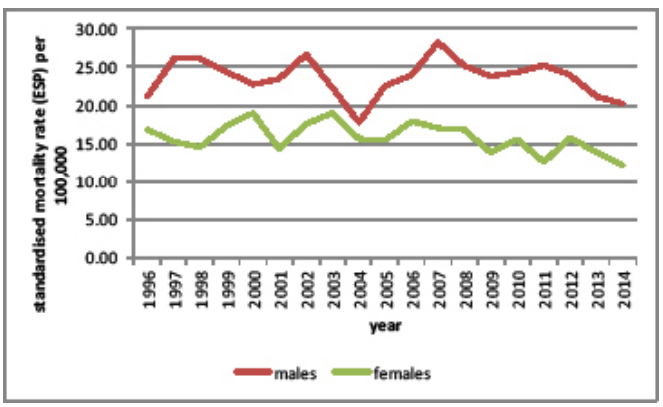


Figure 3. Trends in standardised mortality rate (European Standard Population) in males and females in Malta.[6]

The diagnostic and treatment plan of patients suspected or diagnosed with colorectal cancer is discussed during multidisciplinary team (MDT) meetings which are held once every fortnight at Mater Dei Hospital. Support for the operations of these MDTs will be reinforced to improve their effectiveness and to ensure inclusivity for all patients diagnosed with colorectal cancer. Plans also envisage that the MDTs will eventually assume the role of a tumour management group which will have the responsibility of developing and overseeing the implementation of relevant national care guidelines and monitor and evaluate selected performance outcome indicators.

DISCUSSION AND CONCLUSION

There is large variation in trends in mortality from colorectal cancer in the different European countries, with an average reduction in mortality in EU 27 falling by 13% in men and 27% in women between 1989 and 2011.[11] Countries including the United Kingdom, Austria, Germany and Ireland amongst others showed major reductions in mortality while other countries especially central European countries showed either a small decline or no decline at all.[11] In Malta the overall mean change in mortality in females fell by 15.9% while in males it increased by 5.2% from between 1989 and 2011.[11] Implementation of and participation rates in national screening programmes varies considerably between countries and this is considered to be an important factor in reducing mortality.[12]

The need to target colorectal cancer from prevention, through to earlier diagnosis and advanced treatment protocols is key to improved survival[3] and requires financial resources and well planned cancer strategies.

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1 Systane Ultra, Directions for use Alcon Laboratories, 2012. 2 Systane Hydration, Directions for use Alcon Laboratories, 2015. 3 Systane Gel Drops, Directions for use Alcon Laboratories, 2012. 4 Systane Balance, Directions for use Alcon Laboratories 2012. 5 Rangarajan R, Kraybill B, Ogundele A, Ketelson H. Effects of a Hyaluronic Acid/Hydroxypropyl Guar Artificial Tear Solution on Protection Recovery and Lubricity in Models of Corneal Epithelium. J Ocul Pharmco & Ther. 2015 October 1; 31(8): 491–497.

Alcon A Novartis Division

Mfg Alcon Laboratories, Inc, 6201 South Freeway, Fort Worth, Texas 76134, USA.
EC REP Alcon Laboratories (UK) Ltd. Frimley Business Park, Frimley, Camberley, Surrey GU67SR UK.

SYS Ad2 12/16MT

Cancer control services require a comprehensive approach for the planning, acquisition and governance of the necessary organisational, human, technological and financial resources for the sustainability and further development of the services needed to meet the increasing demand and the dynamic and evolving domains of cancer care. A new National Cancer Plan for Malta is currently being collated and this strategy will include several measures aimed at generating quality improvements at the multiple different phases of the cancer care pathways. Measures will include generic upgrades that will affect all cancer patients such as the implementation of a comprehensive ICT infrastructure that will closely document an individual patient's trajectory, improve connectivity between different care providers and allow the generation of more timely and detailed cancer intelligence. The new National Cancer Plan will also include specific developments that will target the accessibility of increasingly more advanced levels of expertise and technology (including cancer care medicines) for specific cancer groups.

In 2015 the Ministry for Health set up the Cancer Care Pathways Directorate. The aim of this directorate is to develop individualized pathways of excellence in cancer care where the journey of both patients and their families is facilitated in a safe and integrated manner through the provision of holistic care. It also supports, recommends and implements changes within cancer services to ensure high quality services that are delivered in a timely manner.

Support for the patients and their families during this time is an important factor that helps people cope with this challenging condition. The Malta ColoRectal Cancer Awareness Group (MCRCAG - http://www.crc.org.mt/GetSupport) has been set up in February of this year with the aim of creating awareness and education about colorectal cancer as well as support to the patients and their families and caregivers.

Region/Country	1 year	5 year
Northern Europe	79.3 (78.9-79.6)	59.0 (58.5-59.5)
Ireland and UK	72.6 (72.4-72.8)	51.8 (51.5-52.1)
Central Europe	80.5 (80.3-80.7)	60.5 (60.2-60.8)
Southern Europe	78.6 (78.4-78.9)	58.5 (58.1-58.8)
Malta	**74.9 (72.0-78.0)**	**58.1 (53.7-62.7)**
Eastern Europe	69.7 (69.4-70.1)	49.4 (48.9-49.8)

Table 2: 1-year and 5-year relative survival for adult patients with invasive colon cancer diagnosed in 2000-2007[8]

Region/Country	1 year	5 year
Northern Europe	83.4 (83.0-83.8)	59.5 (58.9-60.2)
Ireland and UK	78.5 (78.2-78.7)	53.7 (53.3-54.1)
Central Europe	83.7 (83.5-84.0)	60.1 (59.7-60.5)
Southern Europe	80.4 (80.1-80.7)	55.4 (54.9-55.9)
Malta	**82.1 (78.5-85.8)**	**52.8 (47.0-59.3)**
Eastern Europe	72.4 (72.0-72.8)	44.6 (44.1-45.1)

Table 3: 1-year and 5-year relative survival for adult patients with invasive rectum cancer diagnosed in 2000-2007[8]

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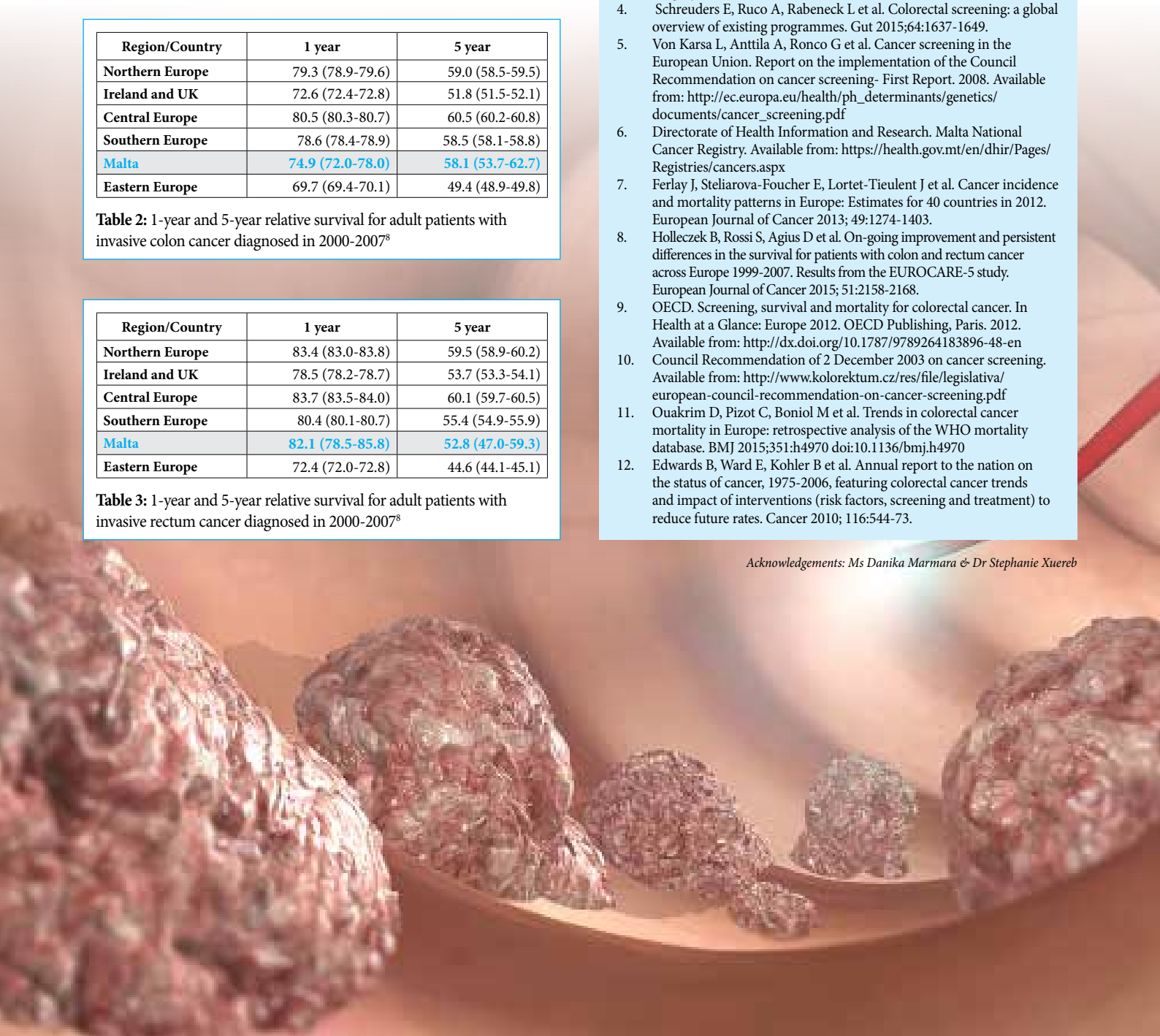

Augmentin® SR

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

gsk

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

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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

CHEMICAL PATHOLOGY IN THE MOVIES: 'LORENZO'S OIL'

MICHELLE MUSCAT

Director: George Miller
Writer: George Miller & Nick Enright
Stars: Nick Nolte, Susan Sarandon, Peter Ustinov
Runtime: 129 min
Release date: 1992

The 1992 medical drama 'Lorenzo's Oil', directed by George Miller, is at the same time a tragic and uplifting movie which deals with one of the lesser known diseases, adrenoleukodystrophy (ALD), which forms part of a subset of diseases of interest to the chemical pathologist. The movie follows the quest and struggle of Michaela and Augusto Odone to save their very own child, Lorenzo, who is found to have this rare condition. The events narrated in this movie are based on a true story, albeit with some alterations made for a movie adaptation.

Adrenoleukodystrophy is an X-linked disorder, hence primarily affecting males, due to a mutation in the ABCD1 gene. This gene encodes a protein in the peroxisomal membrane which is responsible for very long chain fatty acid (VLCFAs) transmembrane transport. In this condition we find elevated levels of VLCFAs. Over the years this disease has also been referred to as Siemerling-Creutzfeld disease, bronzed Schilder's disease, encephalitis periaxialis diffusa, melanodermic type of leukodystrophy, as well as other nomenclature variations that were historically applied. The clinical spectrum may vary significantly, hence making diagnosis more difficult. Males may range from having just adrenocortical insufficiency, adrenomyeloneuropathy, or the childhood cerebral form, for example.[1-7] This last form of the disease is the one illustrated in the film.

Lorenzo is initially depicted in the movie as a bright and vivacious young boy. The very first indication in the film that something is amiss is when the teacher points out to his mother that he is throwing tantrums at school and having 'disturbed behavior'. One of the teachers even recommends he receives special education classes, which his mother insists will be provided at home. In later incidents he falls off his bike, and also falls when reaching out for a decoration on the Christmas tree. The constellation of events leads his parents to seek medical advice. Initial investigations revealed a normal CT scan and EEG and no gross visible neurological abnormality. Later on his mother finds him listening to very loud music and it is discovered that he has hearing impairment. Again, after referral to the appropriate medical specialist, an auditory processing difficulty is confirmed. Further inpatient investigations included tuning fork testing for conductive and sensorineural hearing loss, fundoscopy and further

imaging amongst others. The escalating sense of his parents' desperation is depicted, and climaxes when the diagnosis is provided without equivocation. This is especially so given they were told it is a progressive and relentless disease with a bleak prognosis, and there was no known treatment whatsoever that could be provided to their son at the time. Lorenzo had significantly elevated VLCFAs in his blood. In the movie it is stated that there is a defective enzyme for metabolizing these fats, however this is no longer entirely correct since it is the peroxisomal membrane protein that is defective in ALD patients. The parents are told what 'myelin' is, and are also explained briefly the concept of demyelination. Distraught and in search for answers the father is seen reading literature on the pathology of adrenoleukodystrophy as well as individual case studies. Numerous medical terms were enlarged on screen. Dysphagia, seizures, spasticity, deafness, coma and death were amongst the words highlighted to the viewer on the screen.

The search for a world expert on the leukodystrophies leads them to Professor Gus Nikolais, who was working on a diet for the disease. He suggests enrolling Lorenzo in a trial, and explains to his mother the nature of the genetic transmission of an X-linked disease. It was afterwards noted however that his VLCFAs were increasing rather than decreasing on the initially prescribed diet. Later during the film we see Lorenzo confined to a wheelchair and his family consenting for his case to be used as illustrative example for medical learning. This included his speech impairment, the visual field defects such as hemianopia with transient horizontal nystagmus [without optic atrophy as yet] as well as his characteristic gait which was illustrated when he was asked to walk. The Odone family was also in contact with the ALD Foundation where they met other families with members afflicted with the same disease. Later we are shown the Odones going through biochemistry textbooks and journals and drawing diagrams on their board. Michaela Odone even goes through Polish rat experiments on long chain fatty acid dietary manipulation. The first symposium on ALD was convened through their efforts. Loading the diet with a particular fat to decrease the biosynthesis of another emerged as a leading possibility. After administration of oleic acid, a significant drop in VLCFAs was noted, which eventually plateaued and did not seem to improve any further. The boy's clinical condition later takes an acute turn for the worse, but he miraculously survives the acute episode and the family look further into the literature, and even make a model using different paper clips as carbon atoms. They determine that erucic acid would be a better candidate therapy, however there were challenges in sub-fractionating this from rapeseed oil and getting it approved for human consumption. Finally, after obtaining the desired substance, they tested it out on Michaela's sister, termed jokingly, 'the family rat', and subsequently gave it to Lorenzo. The treatment consisted of an oil containing specific combinations of the triacylglycerol forms of both oleic and erucic acid [hence the name of the movie, Lorenzo's oil]. Upon blood sampling and testing, they were contacted by the laboratory querying possible mislabeling of the specimen, given that the levels of the VLCFAs C24 and C26 were assayed twice and were within normal limits. This held great scientific potential, however in the setting of neurological damage that had already occurred. The movie ends on the note that the father was meeting a group of specialists who were looking into methods to re-myelinate 'the shaking puppy dogs', and the mother tells her child 'if they ever give you back your myelin, you will be able to tell your brain to tell your toes … to do what you want them to do…'. The real life Lorenzo Odone lived up to age 30, which was significantly longer than originally predicted.

Persistence and desperation leads the Odone family to fabricate their very own miracle. The family writes a paper to this effect which was described in the movie as 'a beautiful piece of biochemistry'. This is another movie which shows a personal journey to a medical breakthrough. The author personally highly recommends this movie to those practicing within her medical discipline of chemical pathology or clinical biochemistry as well as those interested in the more research-based pure biochemistry.

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This review is partially funded through the Endeavour Scholarship Scheme.

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

Asthma

Because I simply don't have space for asthma

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

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

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

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

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** *The 92 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV$_1$ <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. *The 184 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. *For COPD:* One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** *Hypersensitivity to* the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/ vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** *Pregnancy:* No adequate data available. *Lactation:* insufficient information available. *Fertility:* There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 *micrograms/ 22 micrograms inhalation powder, pre-dispensed.* **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom **Marketing Authorisation Numbers:** EU/1/13/886/001-6 **DATE OF PREPARATION:** December 2013

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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, Gzira GZR 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]

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MLT.GBVFTT.000116 Date of preparation: February 2014

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Theravance

WITH ULTIBRO® BREEZHALER® EXACERBATION PREVENTION IS IN YOUR HANDS[1]

ULTIBRO® BREEZHALER® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)[2]

FLAME STUDY RESULTS[1]

"... ULTIBRO® BREEZHALER® showed not only non-inferiority, but also... consistent superiority to Seretide®* Accuhaler® for all outcomes related to exacerbations, lung function† and health status**."[1§]

The FLAME study is a 52-week head-to-head trial comparing ULTIBRO® BREEZHALER® with Seretide® Accuhaler® (LABA/ICS) in 3362 exacerbating† COPD patients.[1] The primary endpoint was to demonstrate that ULTIBRO® BREEZHALER® was at least non-inferior to Seretide® Accuhaler® in reduction of all exacerbations. Superiority over Seretide® Accuhaler®* was a pre-defined secondary endpoint.[1]

*Fluticasone/salmeterol 500/50 mcg BID. †Lung function through FEV$_1$ (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] §Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] ¶Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89; P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83; P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87; P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

BID, twice daily; COPD, chronic obstructive pulmonary disease.

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

Ultibro Breezhaler inhalation powder, hard capsules

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

PRESENTATION: Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. **Method of administration** For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta-adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. ***Asthma:*** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. Paradoxical bronchospasm: In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. *Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co-administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp), raises the systemic exposure of indacaterol up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia. **Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc. Representative Office Malta P.O. Box 4, Marsa, MRS 1000 Malta. Tel: +35621222672. 2015-MT-ULT-09-OCT-2015.

References

1. Wedzicha JA, *et al.* Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

ULT Ad1 11/16 MT

NOVARTIS

INTRODUCING ONCE-DAILY SEEBRI BREEZHALER®
AN INHALED ANTICHOLINERGIC FOR PATIENTS WITH COPD.[2]

Seebri Breezhaler 44 micrograms inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION: Each capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 44 micrograms of glycopyrronium.

INDICATIONS: Indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

DOSAGE: The recommended dose is the inhalation of the content of one capsule once daily. Seebri Breezhaler is recommended to be administered, at the same time of the day each day. If a dose is missed, the next dose should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

CONTRAINDICATIONS: ♦ Hypersensitivity to the active substance or to any of the excipients.

WARNINGS/PRECAUTIONS: ♦ Seebri Breezhaler is not indicated for the initial treatment of acute episodes of bronchospasm. ♦ Paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, Seebri Breezhaler should be discontinued immediately and alternative therapy instituted. ♦ Caution in patients with narrow angle glaucoma or urinary retention. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Seebri Breezhaler and to contact their doctor immediately should any of these signs or symptoms develop. ♦ In patients with severe renal impairment including those with end stage renal disease requiring dialysis, Seebri Breezhaler should be used only if the expected benefit outweighs the potential risk. ♦ Seebri Breezhaler should be used with caution in patients with a history of cardiovascular disease. ♦ Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. ♦ There are no data from the use of Seebri Breezhaler in pregnant women. Glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. ♦ The use of glycopyrronium by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. ♦ Glycopyrronium has no or negligible influence on the ability to drive and use machines.

INTERACTIONS: ♦ The co administration of Seebri Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. ♦ No clinically relevant drug interaction is expected when glycopyrronium is co administered with cimetidine or other inhibitors of organic cation transport. ♦ Although no formal drug interaction studies have been performed, Seebri Breezhaler has been used concomitantly with other medicinal products commonly used in the treatment of COPD without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids.

ADVERSE REACTIONS: ♦ Common (≥1/100 to <1/10): Nasopharyngitis, insomnia, headache, dry mouth, gastroenteritis, urinary tract infection. ♦ Uncommon (≥1/1,000 to <1/100): Rhinitis, cystitis, hyperglycaemia, hypoaesthesia, atrial fibrillation, palpitations, sinus congestion, productive cough, throat irritation, epistaxis, dysphonia, dyspepsia, dental caries, rash, pruritus, pain in extremity, musculoskeletal chest pain, dysuria, urinary retention, fatigue, asthenia, hypersensitivity, angioedema.

LEGAL CATEGORY: POM

PACK SIZES: Single pack containing 30x1 hard capsules, together with one inhaler.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom.

MARKETING AUHORISATION NUMBER:
Seebri Breezhaler 44 micrograms inhalation powder, hard capsules - EU/1/12/786/001-008

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

2016-MT-SBR-15-SEP-2016

For information on Seebri Breezhaler dose expression, please refer to full prescribing information.

References: 1. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey [published correction appears in Curr Med Res Opin. 2012;28(8):1405]. Curr Med Res Opin. 2009;25(8):2043-2048. 2. Barnett M. Chronic obstructive pulmonary disease: a phenomenological study of patients' experiences. J Clin Nurs. 2005;14(7):805-812. 3. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37(2):264-272. 4. Novartis Europharm Ltd. Seebri® Breezhaler® Summary of Product Characteristics.

Please see SPC for full prescribing information.

NOVARTIS

Once Daily
seebri®
breezhaler®
glycopyrronium bromide inhalation powder

SEE Ad1 12/16 MT

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 Asthma:* 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 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 ORM 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, Gzira GZR 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: Hand-Haled 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.GlbRESP/0004/14 Date of preparation: Feb 2014

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CHOLESTEROL & STATINS

THE CONTROVERSY CONTINUES

ALBERT CILIA-VINCENTI

A recent widely publicised Lancet review of statin efficacy and safety data generated more controversy than it resolved.[1] Led by Professor Rory Collins of Oxford University, the review claimed that the benefits of statins have been underestimated and the risks exaggerated. Claims of statin intolerance in up to 20% of patients, the review argues, are not supported by large-scale evidence from randomised trials. In fact, Collins et al. claim that statin therapy is no less well tolerated than placebo.

Collins further claimed that the controversy about statin intolerance and myopathy rates emerged only in the past 2 or 3 years as manufacturers began marketing newer and "very expensive" cholesterol-lowering agents, such as, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for patients classified as statin intolerant. He also pointed out that industry has funded reports on statin intolerance, as in the case of the European Atherosclerosis Society's report[2] which, not only had funding from makers of PCSK9 inhibitors, but also had its meetings coordinated by a commercial entity funded by the manufacturers.

Collins claimed that one could expect that 5 years of a statin regimen that lowered LDL cholesterol by 2mmol/L would prevent major vascular events in about 1000 of 10,000 secondary-prevention patients and about 500 of 10,000 primary-prevention patients, with a bigger benefit to be expected with lifelong statin use. Moreover, he added, whereas many of the adverse effects (such as myopathy) can be reversed with no residual ill-effects by stopping the statin, the effects of a heart attack or stroke are often irreversible.

Dr Harlan Krumholz (Yale University), commenting on the review in the BMJ,[3] said that while the findings strongly support the benefits of statins in comparison to modest risks, there is little consideration of the limitations of the trial evidence, most notably a lack of robust data on elderly patients, individual trials whose design prevented detection of many relevant harms, and inconsistent methods for adverse event data collection.

A vocal critic of the review, and an author of one of the 2013 BMJ papers,[4] Dr Aseem Malhotra (Lister Hospital, Stevenage, UK) claims that the Clinical Trials Service Unit at Oxford has received hundreds of millions of pounds in funding from statin manufacturers and that Collin's group has not released raw data on the major statin randomised controlled trials for independent scrutiny. He adds that by using predominantly industry-sponsored trials designed for the purpose of determining the benefits of statins but minimising side-effects, this review simply adds false precision to biased estimates. He also noted that Pfizer's own patient leaflet on atorvastatin states that common side-effects possibly affecting up to one in 10 people include sore throat, nausea, digestive problems, muscle and joint pains.

Malhotra has also co-authored a recent systematic review revealing that in those patients over age 60, LDL-cholesterol is not associated with cardiovascular disease and is inversely correlated

with all-cause mortality.[5] He is quick to admit that statins have a benefit, but adds that focusing on LDL lowering as if this was the end in itself is counterproductive, especially when insulin resistance is a more important risk factor for myocardial infarction. He concludes that in his view, the Lancet review is a total whitewash, and agrees with the BMJ's editor-in-chief, Fiona Godlee, who described it as "the trialists making their own homework".

It turns out that Godlee and Collins have been at odds ever since Collins called on the BMJ to correct and ultimately withdraw the two 2013 studies that repeated claims made in a paper by Abramson et al.[6] that side-effects of statins occur in 18% to 20% of people. The BMJ corrected the statements in the two studies, but Godlee passed the decision, on whether to retract, on to an independent expert panel, which rejected Collins's request for retraction in June 2014. In October 2014, Collins and other co-authors of the new Lancet review, sent a letter of complaint about the BMJ's handling of the two papers to the UK's Committee on Publication Ethics (COPE). In April 2016, COPE determined that the BMJ acted with due diligence and in line with the expectations under the COPE Code of Conduct.

The Lancet editor-in-chief Dr Richard Horton, however, in a comment accompanying the statin review,[7] calls into question the independence of the BMJ-appointed panel's judgement, noting that the chair had previously written critically about statin use among older patients. Horton observed that more than 200,000 patients were estimated to have stopped taking a statin in the 6 months after adverse media coverage following publication of the disputed research, and drew parallels between "this statin scare" and the MMR vaccine scare that began with a now-retracted research paper that had led to widespread vaccine hesitancy.

Horton's comment about COPE's conduct prompted Godlee's rapid response letter[8] of 14th September 2016, that COPE did not decline to act but deliberated on the concerns raised by Collins et al., and on the BMJ's response, and came to a clear conclusion that the BMJ had acted appropriately. Godlee has also written to England's chief medical officer asking for an inquiry into the statins saga and for an independent review of the evidence on statins. She claims that an independent third-party scrutiny of the statins trial data remains an essential next step if this increasingly bitter and unproductive dispute is to be resolved.

TAKE HOME MESSAGES

1. Apart from the above claims of drug-company funding and dubious research quality, the Lancet review in question, penned by several professors of medicine and cardiology, is flawed for at least another two reasons. One is the fact that all the data is based on routine LDL measurements. Previous instalments in this Synapse series have put forward evidence for LDL having two biologically different sub-fractions – a large light particle LDL and a small dense particle LDL – with only the latter being related to atherosclerosis. Routine LDL measurements do not indicate whether moderately raised LDL is due to a raised large or small sub-fraction. The surrogate marker for a raised small LDL sub-fraction is raised triglyceride (TRG) combined with low HDL – **the higher the TRG/HDL ratio, the higher the risk for atherosclerotic disease.**
2. Another flaw in the review is the persistent belief that the benefit of statins is via their blood lipid–lowering action. It is now well-established that the essence of atherosclerosis is an inflammatory disease of arteries. Statins are now recognised to be potent anti-inflammatory-cytokine agents, and their clinical benefit is mainly via this anti-inflammatory route. The high-sensitivity C-reactive protein (HsCRP) is the other valuable measurement of possible atherosclerotic inflammatory activity, particularly when combined with the TRG/HDL ratio.
3. As pointed out above by Dr Aseem Malhotra, insulin resistance (chronic hyperinsulinaemia) is a more potent indicator of myocardial infarction risk than LDL. This has been highlighted in a previous instalment of this Synapse series, which also pointed out that the TRG/HDL ratio is a surrogate marker for insulin-resistance/hyperinsulinaemia. Some private laboratories in Malta will be adopting the TRG/HDL ratio and the HsCRP as the main markers of atherosclerotic activity risk.

REFERENCES

1. Collins R, Reith C, Emberson J, et al. Interpretation of evidence for the efficacy and safety of statin therapy. Lancet 2016; 388: 2532-61.
2. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy: European Atherosclerosis Society Consensus Panel Statement on assessment; aetiology and management. Eur Heart J 2015; 36: 1021-22.
3. Krumholz HM. Statins evidence: When answers also raise questions. BMJ 2016; 354: i4963.
4. Malhotra A. Saturated fat is not the major issue. BMJ 2013; 347: i6340.
5. Ravnskov U, Diamond DM, Hama R, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: A systematic review. BMJ 2016; 6: e010401.
6. Abramson JD, Rosenberg HG, Jewell N, et al. Should people at low risk of cardiovascular disease take statin? BMJ 2013; 347: 16123.
7. Horton, R. Offline: Lessons from the controversy over statins. Lancet 2016; 388: 1040.
8. Godlee F. Rapid response re COPE complaint. BMJ 2016; Letter (14 September).

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

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

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

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

Help Poppy by prescribing Seretide

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

Safety Information

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

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

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

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

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

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. As 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. As monotherapy 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 thiazolidinedione 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 U.L.N. 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 3xU.L.N 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 (glibenclide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, warfarin 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, asthenia, hyperhidrosis, asthenia. Uncommon: fatigue. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. Combination with Thiazolidinedione: Common: weight increased, 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 and 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/1/07/410/001, 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, Sliema SLM3 1000, Malta. Tel: +356 21222872. 2015-MT-GAL-16-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 metformin 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 with metformin and a sulphonylurea: The dose 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 acidic acidosis, renal function should 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 restarted 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, warfarin 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 medicinal products having a glycaemic 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/1/07/410/005-008, 013. **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, Sliema, SLM3 1000, Malta. Tel: +356 21222872.2015-MT-EUC-16-DEC-2015

GAL AD2 12/16 MT

NOVARTIS

Galvus vildagliptin

Eucreas vildagliptin/metformin

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

HIV AND AIDS

MPSA

JESSICA ZARB

HIV

HIV (human immunodeficiency virus) is a virus that gradually attacks the immune system. The body finds it harder and harder to fight off common infections as the disease gradually progresses. The virus destroys white blood cells (CD4). These cells are responsible for combating infections; another name for them is T-lymphocytes.

There are many different strains, someone who is infected may carry different strains in their body. The two main types are HIV-1 and HIV-2. HIV-1 is the most common type found worldwide whereas HIV-2 is limited to Western Africa, with very few cases in India and Europe. Symptoms make take around 10-15 years to emerge and by then the HIV would have already caused significant harm to the immune system.

HIV is found in the following body fluids of an infected person: semen, blood, vaginal secretions and breast milk. Risk of infection is increased when using infected needles, syringes or any other methods which include the crossover of blood. It is spread primarily by unprotected sex. HIV, however, cannot be transmitted through saliva, sweat or urine.

AIDS

AIDS (acquired immune deficiency syndrome) is a syndrome caused by the HIV virus. AIDS develops when the HIV infection has significantly progressed. This is the last stage of HIV infection where the body can no longer defend itself and may thus develop various diseases. These include pneumonia, fungal infections and any type of opportunistic infection. There is also an increased risk of developing other life-limiting conditions including cancer and brain illnesses.

Methods of prevention: safe sex; no sharing of any instruments in contact with blood.

There is currently no cure for HIV or AIDS. However with the right treatment and support, patients can live long and healthy lives.

NO NEWS... IS GOOD NEWS!

The doctor took his patient into the room and said
'I have some good news and some bad.'
'Give me the good news' said the patient.
'They're going to name a disease after you!' replied the doctor.

ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE[1] CLASS I RECOMMENDED[1,3]

Change your symptomatic HFrEF patients to ENTRESTO®

- **Activates the heart's beneficial response** by enhancing the natriuretic peptide system, while maintaining RAAS inhibition[5,6]
- **20% reduced risk** of first CV death or heart failure hospitalisation vs enalapril ($P<0.0001$; ARR=4.7%)[5‡]
- **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) Presentations: 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, divided 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 ACEI, 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: 34 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. Else 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 transient difference of 5 bpm in heart rate compared to the administration of nitroglycerin 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, GU16 7SR, 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 3844, Entresto 97 mg/103 mg film-coated tablets EU/1/15/1058/003- 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, Pro Doc 4, Marsa, MRS 1003, Malta. Tel: +356 21222872. PHM MT ENT 16 JUN 2016

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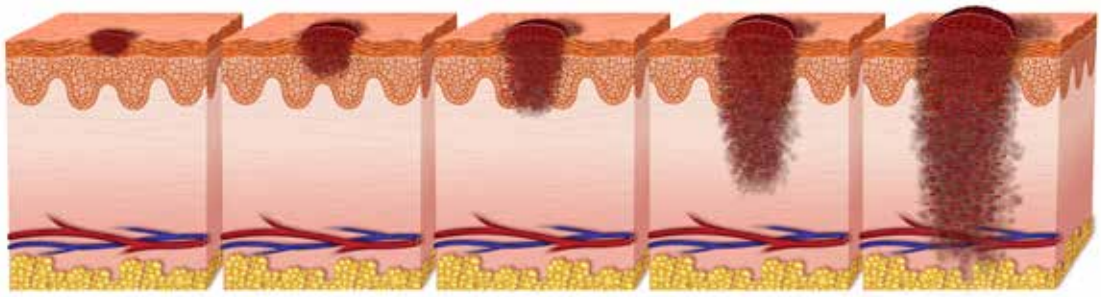
METASTATIC MELANOMA:

HOW DO LOCAL TREATMENT OPTIONS COMPARE WITH CURRENT STANDARDS OF CARE?



INTERVIEW WITH
DR NICHOLAS REFALO

Of all skin cancers, metastatic melanoma is the deadliest form. Early diagnosis allows it to be cured with surgery alone; later presentations considerably limit successful treatment options. Dr Nicholas Refalo, Consultant Oncologist at Mater Dei Hospital, explains to Dr Gabriel Ellul the toll which metastatic melanoma has on the Maltese population, and the current treatment options available.

TS: WHAT IS METASTATIC MELANOMA?

Melanoma is the malignant proliferation of melanocytes. As in all malignant growths, it is classified into stages depending on its degree of spread. Metastatic melanoma relates to stage IV of the disease, with metastatic spread to multiple organs, most notably lungs, liver, brain and bone. Spread occurs primarily via the lymphatic system, with haematogenous spread either arising secondary to the lymphatic dissemination of the tumour, or else once the tumour directly invades the vascular system.

A distinguishing and morbid aspect of stage IV melanoma is its poor survival rate with the 10-year survival rate being, at best, less than 10%. At this advanced stage of disease, the role of surgery and radiation is limited, and the only viable options are systemic treatment modalities.

TS: WHAT CAUSES THE DISEASE?

The aetiology of melanoma is a widely studied subject, with the principal causative factors being exposure to UV light and a genetic predisposition, amongst others. Additionally, there are a multitude of risk factors which decrease the overall survival rate, including older age, poor performance status at time of diagnosis, male gender, multiple metastatic sites, shorter disease-free intervals, leukocytosis, and neutrophilia prior to initiation of treatment.

Melanoma, in its aetiology, may arise from a number of different sites, with this forming the basis in the genetic variability of melanoma. Four distinct genetic types have in fact been identified: melanoma arising from normal skin without any preceding sun exposure; that arising from skin which had undergone chronic exposure to UV irradiation; melanoma arising from the soles of feet or the palms of the hands; and melanoma derived from mucosal surfaces.

This distinction has served to direct certain gene-based treatment modalities.

TS: HOW DOES ADVANCED MELANOMA MANIFEST ITSELF AND HOW COMMON IS IT?

These patients usually present with multi-organ involvement, mostly with metastases to the lungs, liver, brain and bone. Locally, metastatic melanoma accounts for up to 10 new cases a year. They are usually referred with curative intent, but current treatment options provided by the public health care system allow only palliation at the very best.

TS: HOW SO? WHICH TREATMENTS ARE AVAILABLE LOCALLY?

Locally we make use of dacarbazine, an alkylating agent approved by the FDA in 1975 - more than 4 decades ago. Patients on this drug only have a one-in-eight chance of tumour shrinkage.[1] In fact, an analysis of a total of 23 RCTs concluded that the objective response rate for monotherapy with dacarbazine hovers around 15%.[2]

Furthermore, responses are rarely sustained, with fewer than 2% of patients with metastatic melanoma, treated with dacarbazine, surviving for more than 6 years.[3] Consequently, the primary purpose of dacarbazine is palliation, not treatment, of metastatic melanoma.

Despite these shortcomings, dacarbazine remains the only form of chemotherapy funded by our healthcare system here in Malta. All other options, available abroad, require private funding.

TS: HOW DOES THIS COMPARE TO CURRENT STANDARDS OF CARE?

In view of the poor survival rates with the available chemotherapeutic modalities, as evidenced by data supporting dacarbazine, there has been a shift towards immune-mediated therapies and targeted therapies in Europe.

Over the past decade, with an enriched understanding of the pathogenesis of melanoma, novel therapies have been adopted in a multitude of European countries, which have had a profound impact on the survival rates of patients with metastatic melanoma.

These most notably include a drug called ipilimumab, an immunomodulator targeting the function of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4).

Activated T-lymphocytes express this antigen, which in turn hinders positive stimulatory signals directed towards them. Thus, CTLA-4 acts negatively, to inhibit T-cell activation in the healthy individual.

Ipilimumab acts against CTLA-4. As a monoclonal antibody, it inhibits it and thus obtunds its inhibitory effect on T-cell activation, thereby indirectly prompting the T-cell mediated immune system to counter cancer more effectively.

Response rates to ipilimumab are encouraging. A phase III trial on previously treated, unresectable advanced melanoma showed an overall rate of survival of 45.6% after 12 months of therapy, and 23.5% after 24 months of ipilimumab monotherapy. Such trials also compared the efficacy of this monoclonal antibody when given in combination with vaccination strategies, producing even more favourable results.[4]

These results have prompted the FDA to expedite its approval of ipilimumab as a treatment modality for metastatic melanoma in March 2011, after more than a decade without any pharmaceutical innovation in the field.

The response rates to dacarbazine pale in comparison to the results achieved through this novel treatment.

And while these results are encouraging, the same can be said to another treatment strategy which is currently being given much attention through research and clinical trials. As outlined previously, melanoma has been classified into four distinct genetic subtypes. Of those melanomas developing from normal skin, like the thighs and trunk, which has not been exposed to chronic insolation, around 60% have a mutation in the B-RAF gene.

The B-RAF gene acts as a proto-oncogene, with gain-of-function mutations allowing it to promote cell growth and division unchecked. The rationale behind targeted therapies is to shut down these genes, thereby annulling their positive effect on tumour growth.

The results obtained with such an approach are astounding: major shrinkage of advanced melanoma tumours was obtained through the use of a drug called PLX4032, with positive response rate in over 80% of treated patients.[5] And while most of these patients eventually suffered from melanoma recurrences, prompting the need for future studies of possible combination therapies making use of this novel drug, the results speak for themselves.

Similar approaches are also being adopted for the different genetic subtypes, with ongoing research on potential inhibitors of the KIT proto-oncogene, which also plays a significant role in the aetiology of advanced melanoma.

TS: WHAT ARE YOUR VIEWS ABOUT THE DIFFERENCE IN RESPONSE AND SURVIVAL RATES BETWEEN THESE NOVEL THERAPIES AND THE ONES ON THE GOVERNMENT FORMULARY?

To this day, dacarbazine remains the only systemic therapy available for advanced melanoma patients on the government formulary. And as discussed previously, the response rates for dacarbazine do not, in any way, match those obtained through the novel treatments available today.

As things stand, I feel confronted with the difficult situation of informing my patients that the only available "cure" afforded to them through the public health system is one which has nowadays been all but superseded by drugs which are not part of the formulary. The best I can offer them, presently, is dacarbazine, a drug which is palliative and not curative.

The price for immunotherapy or targeted therapy ranges in the tens of thousands of euro a month, with an estimated yearly cost of more than €120,000 for 12 months of therapy, despite discounts by the local pharmaceutical companies.

We are currently in a situation where advanced melanoma patients in Malta, who have a modest level of income, cannot afford basic curative treatment, which is otherwise available in other European countries.

Oncological centres across Europe, from well-established centres in Western Europe to less developed countries such as Albania, have made the necessary shift: they are treating their patients with these novel drugs for advanced melanoma, thus affording them a better chance of recovery.

TS: WHAT ARE YOUR CONCLUDING REMARKS?

The situation is in a dire need for change.

In the present state of affairs, all Maltese patients diagnosed with advanced melanoma have only two options: either buy this costly medication or else ask for help from local charitable institutions.

The former is a viable alternative only to those who are insured or else have the necessary financial means. With regards to the latter option, we cannot constantly rely on charity to provide for the needs of these patients. If these two options fail, the chances of successful recovery from advanced melanoma remain very, very slim.

The annual incidence rates of advanced melanoma may not be as high as in other, more well-known forms of cancer. However, we have a duty to each of our patients.

I believe that this situation warrants more public exposure; there is a need for greater public advocacy on the issue. That is why I have decided to speak up.

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PIERRE VASSALLO

ULTRASOUND DIAGNOSIS AND MANAGEMENT OF ECTOPIC PREGNANCY

Ectopic pregnancy is defined as the presence of a gestational sac outside the uterine cavity and has a prevalence of approximately 2%. Ninety-five percent of ectopic pregnancies occur in the non-interstitial portion of the fallopian tube (infundibulum, ampulla or isthmus) (Fig 1). The main presenting features of an ectopic gestation are vaginal bleeding and abdominal/pelvic pain occurring during the first trimester of pregnancy; a prevalence of ectopic pregnancy of up to 18% has been reported for women presenting with these symptoms. Transvaginal Ultrasound (TVUS) combined with serial measurement of serum Human Chorionic Gonadotrophin (HCG) are the tools used for the diagnosis and management of ectopic pregnancy.

The possible locations of an ectopic pregnancy follow the normal course of the developing oocyte / fertilised ovum starting in the ovary, followed by release into the peritoneal cavity through ovulation and subsequent transit through the fallopian tube to reach the uterine cavity. In addition, an ectopic pregnancy may occur in the cervix or in a caesarean scar.

There are no reliable findings on pelvic ultrasound during the first 5 weeks of gestation. At 5 weeks gestational age, a 2-3mm gestational sac is generally seen in the endometrial lining of the uterus (Fig 2); the endometrial lining during gestation is known as the decidua and the presence a sac within it is called the intradecidual sac sign. At 5.5 weeks, a yolk sack appears (Fig 3). At 6 weeks, a 10mm gestational sac, a foetal pole and cardiac pulsations are generally evident (Fig 4). If none of these findings are present in a patient with a positive pregnancy test, serial Beta HCG testing and a repeat ultrasound in 7 days are indicated until the location of the pregnancy is identified.

An intradecidual sac may also occur with an early ectopic pregnancy, where it is known as a pseudogestational sac; this represents a small fluid collection within the decidua that mimics a gestational sac. A more reliable ultrasound finding to help differentiate a pseudogestational sac from a gestational sac is the presence of the double decidual sac sign; this sign is the result of minimal fluid present between the decidual capsularis and the dedicual parietalis around the portion of the sac that is opposite the foetal pole (Fig 5).

Decidual cysts are the result of degeneration of decidual cells producing a thin walled, fluid filled cavity (Fig 6). A decidual cyst is located at the myometrial/endometrial

junction in early first trimester pregnancy, which contrasts with a pseudogestational sac that lies centrally within the endometrium. Decidual sacs may occur in intrauterine and extrauterine pregnancies and in non-pregnant women. They may also occur centrally within the placenta in later pregnancy frequently close to the point of cord attachment; they are only of concern when measuring >3cm in diameter, when they must be distinguished from villous infarcts.

To safeguard a possible wanted pregnancy, the Society of Radiologists in Ultrasound established criteria in 2013 for a nonviable first trimester pregnancy. Primarily they state that any round or oval fluid collection in a woman with a positive pregnancy test result is most likely, and should be reported as, an intrauterine pregnancy. Findings indicative of a non-viable pregnancy include (1) an embryonic crown-to-rump length ≥7mm and no heartbeat, (2) a mean gestational sac diameter of 25mm and no embryo, (3) absence of a heartbeat ≥2 weeks after detection of a decidual sac (4) absence of a heartbeat ≥11 days after detection of a decidual sac containing a yolk sac. These criteria may also be used to identify a pseudogestational sac in the presence of a rising beta HCG level.

An ectopic pregnancy usually presents around 5-6 week following the last menstrual period with vaginal bleeding and abdominal or pelvic pain if it is in a tubal location. Intraabdominal, ovarian or interstitial ectopic pregnancy may present later. More than 50% of women with tubal pregnancy present with tubal rupture resulting in haemoperitoneum and shock. Spontaneous resolution of a tubal pregnancy has been reported to occur in 5-24% of cases.

The absence of an intrauterine gestational sac at 5-6 weeks gestation should prompt measurement of serum beta HCG levels. Beta HCG levels increase more slowly in the case of ectopic pregnancy. In the case of a viable pregnancy, a rise beta HCG levels of at least 66% should be observed within 48 hours. An increase in beta HCG level of <53% in 48 hours is usually a sign of a non-viable pregnancy with a 99% sensitivity. Despite the increase in beta HCG levels during the first trimester, there is a wide range of normal values (Fig 7). Therefore, a single beta HCG value is of no value for diagnosing a viable, non-viable or ectopic pregnancy. Serial beta HCG measurements are required.

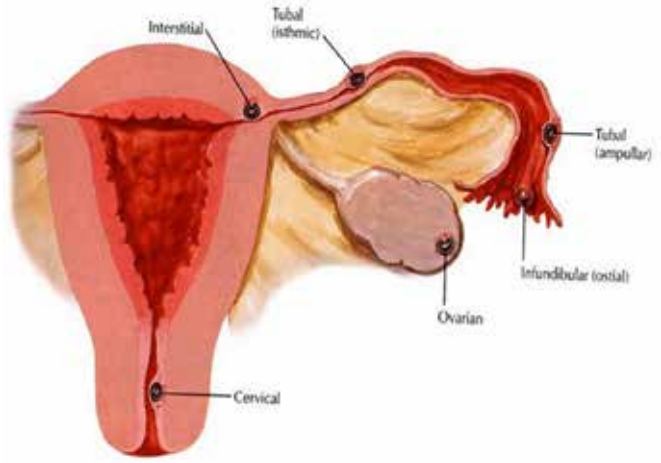

Figure 1: Ectopic pregnancies most frequently occur in the non-interstitial portion of the fallopian tube, which is composed of the infundibulum, ampulla or isthmus. Less commonly, an ectopic pregnancy may occur in the interstitial (intramyometrial) portion of the tube, in the ovary, in the cervix, in a caesarean scar or in the abdominal cavity.

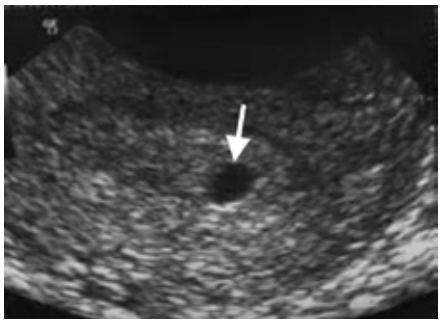

Figure 2: TVUS showing a 5-week gestational sac (arrow) measuring 3mm in diameter located in the endometrium (positive intradecidual sac sign).

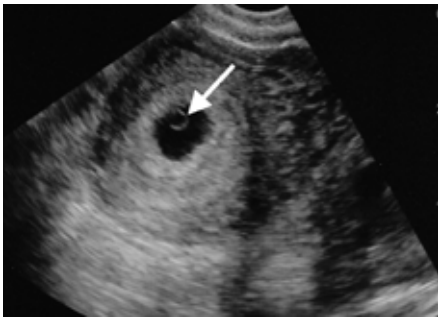

Figure 3: TVUS showing a 5.5-week intrauterine gestational sac containing a yolk sac (arrow).

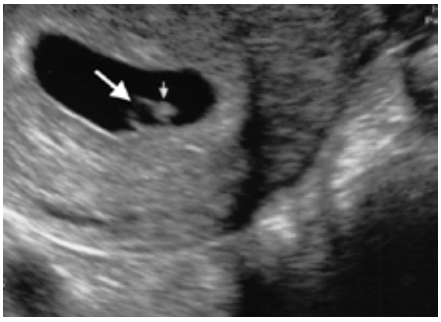

Figure 4: TVUS showing a 6-week intrauterine gestation containing a yolk sac (large arrow) and a foetal pole (small arrow).

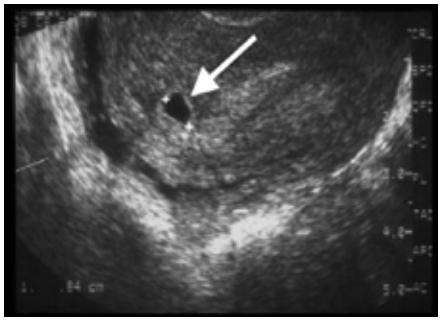

Figure 5: TVUS showing a decidual cyst (arrow) showing thin walls and located at the endometrial/ myometrial junction.

Risk factors for developing an ectopic pregnancy include a previous ectopic gestation, prior tubal surgery or ligation, a prior caesarean section, previous myometrial or endometrial surgery, in vitro fertilisation, a history of endometriosis, the presence of an intrauterine contraceptive device, pelvic inflammatory disease, congenital uterine anomalies (may occur with a history of intrauterine diethylstilboestriol exposure) and smoking.

The most specific (100% specificity) for an extrauterine pregnancy is the finding of an extraovarian mass containing a sac with a live embryo (with heartbeat), however this is rarely seen. More commonly a tubal ectopic pregnancy presents on TVUS as an extra ovarian extrauterine mass containing a gestational sac surrounded by an echogenic ring (Fig 8); there is increasing specificity if a yolk sac, embryo and a heartbeat are present. Increased vascularity around the sac on Doppler ultrasound (known as the Ring-of-Fire sign) and the presence of small amount of ascites are not reliable signs. The presence of more abundant peritoneal fluid containing blood components is a more reliable sign of an ectopic gestation.

An interstitial tubal ectopic pregnancy refers to a pregnancy located in that portion of the fallopian tube that runs through the myometrium. This portion of the tube has greater dispensability, so sign of an interstitial ectopic pregnancy may present later (as late as 16 weeks). The signs of an interstitial ectopic pregnancy include a thin myometrial cover and an eccentrically located gestational sac (Fig 9). However, this must be distinguished from an angular pregnancy, which is in the uterus close to the entry point of the fallopian tube and is viable pregnancy.

Cervical pregnancies occur about 3-4 times more frequently following vitro fertilisation treatment than in normally conceived pregnancies. The gestational sac is usually located in the proximal cervical canal (Fig 10) and must be distinguished from a spontaneous abortion in progress. On TVUS, pressure applied on the cervix by the endovaginal probe results in a sliding movement of the gestational up and down the cervical canal in the case of an abortion in progress. This movement is absent in a cervical ectopic pregnancy.

Heterotopic pregnancies are multiple pregnancies that occur simultaneously in both an intrauterine and an ectopic location (Fig 11). These are most commonly seen in women receiving assisted reproductive treatments. In such cases, the ectopic gestation sac may be treated with laparoscopic removal or image-guided ablation.

Understanding the imaging findings in women with ectopic pregnancies is crucial as it helps guide early management. The risk of incorrect diagnosis of an ectopic pregnancy are high and may result in maternal exsanguination and death.

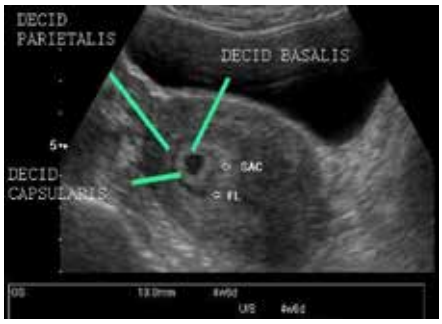

Figure 6. TVUS showing a thin film of fluid (FL) separating the decidua capsularis from the decidual parietalis and forming the double decidual sac.

Weeks since LMP	Approximate hCG Range (mIU/mL)
4 weeks	0–750
5 weeks	200–7000
6 weeks	200–32,000
7 weeks	3000–160,000
8–12 weeks	32,000–210,000
13–16 weeks	9000–210,000
16–29 weeks	1400–53,000
29–41 weeks	940–60, 000

Figure 7. Range of normal beta HCG values at different stage of gestation. Not the increasing values occurring during the first trimester.

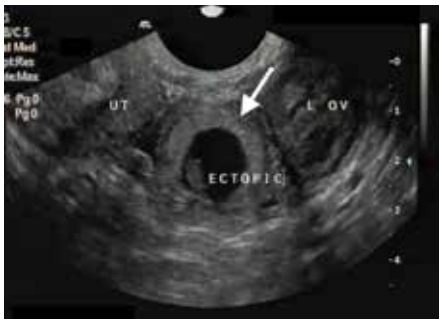

Figure 8. TVUS showing the uterus to the left (UT), left ovary to the right (L OV) and an tubal ectopic gestation (Ectopic). Note the echogenic ring (arrow) surrounding the sac.

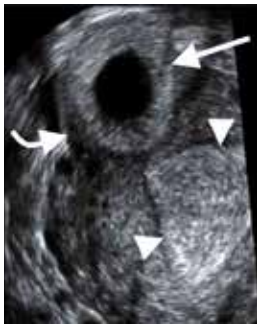

Figure 9. TVUS showing an interstitial ectopic pregnancy (arrow) with thin overlying myometrium (curved arrow). Note the normal endometrium (arrowheads).

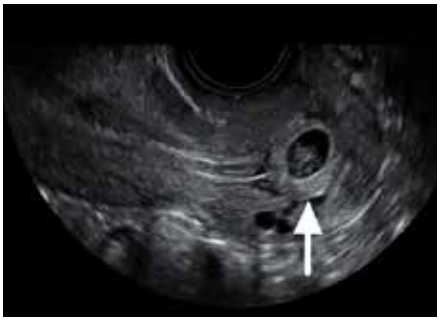

Figure 10. TVUS showing a gestational sac (arrow) in the proximal cervical canal.

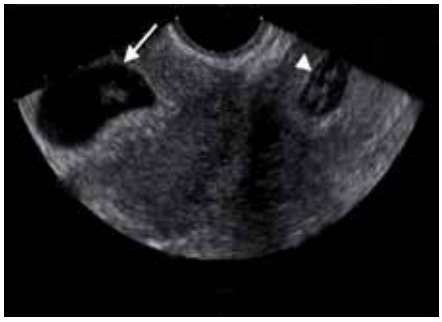

Figure 11. TVUS showing a normal intrauterine gestational sac (arrow) and a tubal gestational sac (arrowhead).

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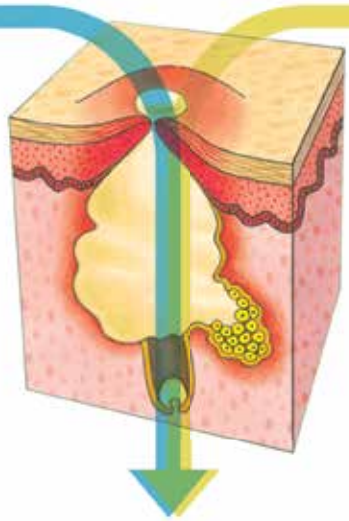

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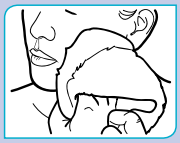

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Duac® Once Daily 10mg/g + 50mg/g Gel Abridged Prescribing Information

**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)

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)

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

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%

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