1996 20YEARS 2016

thesynapse.net

THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- Update on eHealth developments in Europe
- Zika Virus: a global health threat
- The revised ESC guidelines on Heart Failure - An update
- Update on Sirtuins: Is there any Clinical Relevance?

Volume 15, 2016 Issue 04

ISSN number 2313-8084

A maintenance bronchodilator treatment for patients with COPD who are breathless

ANORO™ ELLIPTA™

umeclidinium/vilanterol

breathe...

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

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

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

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

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

REPORTING ADVERSE EVENTS (AEs):

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

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

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

BREXIT & UK'S NEGATIVE FLYNN EFFECT

EDITORIAL

On average, IQ test scores worldwide are on the increase. This means that younger generations perform better than older ones. This is called the Flynn effect, named after Prof. James Robert Flynn at the University of Otago in Dunedin, New Zealand who extensively researched this subject.

Flynn's initial 1984 study[1] revealed a 13.8-point increase in IQ scores in the US population between 1932 and 1978, amounting to a 0.3-point increase per year. This phenomenon was confirmed in other countries including Canada and different European nations, although the rate increase seemed to vary according to country and type of IQ test conducted.

The Flynn effect implies that an individual will likely attain a higher IQ score on an earlier version of the same IQ test rather than on the current version (IQ tests are updated periodically). There are multiple hypotheses for the Flynn effect, including improved nutrition, better education and employment and a more stimulating environment. It is noteworthy that today, more adults are accessing better education, including scientific subjects. These involve testing a hypothesis, using abstractions and using the latter logically. In tandem, employment is also becoming cognitively more flexible. A family doctor living a couple of decades ago did not have access to today's technological armamentarium. And do you imagine a 19th century banker coming up with the infamous credit default swaps and collateral debt obligations (these heralded the recent economic recession which we are still experiencing today).

Other interesting theories supporting the Flynn effect include contraception and the eradication of childhood diseases. Contraception has led to smaller families in recent decades. This means that having for example two children rather than a dozen or so which our grandmothers bred, in turn provides for more adult-child interaction, attributed to lead to enhanced stimulation of the mind, better communication skills and higher IQ. On the other hand, the reason as to why the eradication of childhood diseases seems to improve IQ is that from an energetics standpoint, a sick child will have difficulty developing a brain in view of the fact that convalescence and ontogenesis of the brain are both very taxing metabolically.

However, interestingly, since the mid-1990s we are experiencing a decline in the average IQ in France, Norway, Denmark, Australia, Sweden and the Netherlands. This was also found in the UK.[2] This may be partly caused by the large numbers of non-European immigrants [attributed to have lower IQs[3]] who settled in these countries from the mid-1960s onwards. As an example, at the end of the first decade of the 21st century, 13.1% of the Norwegian population were non-European, as were 11.4% in Denmark, 21% in the Netherlands, 11% in the UK, and approximately 20% in Australia. These non-Europeans, with the exception of the Chinese, have average IQs ranging from 10 to 30 points lower than the European average.[3] This could partly explain the decline in IQs in Western European nations.

Interestingly, following a study conducted between 1997–2009, this so called negative Flynn effect has also been reported in Finland even though the influx of immigrants during that period was small. In this case, dysgenic fertility is probably to blame. Dysgenic fertility relates to the environmental influences that cause more intelligent people to have fewer children and less intelligent people to have more children, possibly arising from the manner in which welfare systems are established.

The UK thus seems to experience a declining IQ score, which is reportedly partly attributed to the cohort of *naturalised non-European* immigrants.[3] The question which I ask is whether this contributed, to some varying extent, to the 6.8% swing in the recent Brexit referendum in favour of the *Leave* campaign (which effectively pledged to curb migration from within the European Union). Against this backdrop, it is worthwhile factoring the surprising allegiance which was pledged by a significant segment of immigrants to Marine Le Pen, the xenophobic leader of the conservative political party in France. Further analysis on this effect is warranted.

REFERENCES

1. Flynn JR. The Mean IQ of Americans: Massive Gains 1932 to 1978. Psychol Bull. 1984; 95(1):29-51.
2. Shayer M, Ginsburg D, Coe R. Thirty years on - a large anti-Flynn effect? The Piagetian test Volume & Heaviness norms 1975-2003. Br J Educ Psychol. 2007;77(Pt 1):25-41.
3. Lynn R,Vanhanen T. Intelligence: A Unifying Construct for the Social Sciences. London: Ulster Institute for Social Research; 2012.

Cover: Bighi Royal Naval Hospital, Kalkara. Lithograph of L. Brocktorff
Bighi Hospital contributed to the nursing and medical care of casualties whenever hostilities occurred in the Mediterranean, contributing in making Malta "the Nurse of the Mediterranean". Today it houses the Malta Council for Science and Technology.

Photo Credit: MCST

Editor-in-Chief: Dr Wilfred Galea
Managing Editor: Dr Ian C Ellul
Sales & circulation Director: Carmen Cachia

Email: mpl@thesynapse.net
Telephone: +356 21453973/4

Publisher:
Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street, Dingli
Malta, Europe

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

GMS GERMAN-MALTESE MEDICAL SOCIETY

MMSA

MPSA

MADS Malta Association of Dental Students

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

Annual subscription rates outside Malta: Six issues €90 or equivalent, worldwide

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

Asthma

Because I simply don't have space for asthma

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

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

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

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

Please refer to the full Summary of Product Characteristics before prescribing

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

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

REPORTING ADVERSE EVENTS (AEs):

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

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

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

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

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

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

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

gsk

Theravance

AUTHORS

Professor Albert Cilia-Vincenti MD FRCPath is a private consultant pathologist in Malta and Chairman of the Academy of Nutritional Medicine (London) and former scientific delegate to the European Medicines Agency (London). He is a former pathology services director to the British and Maltese health services, and a former teacher of London and Malta Universities. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 27 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-author of the article is Dr Michael Balzan.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Health, Malta.

Dr Hugo Agius Muscat MD MSc is a Consultant in Public Health Medicine in the Ministry for Health and a visiting senior Lecturer at the University of Malta. He has worked in health informatics since 1988.

Dr Kirsten Schembri MD graduated from the University of Malta in 2014. She is a second-year Foundation Doctor and is currently following a three-year distance learning course leading to the award of MSc in Internal Medicine with the University of Edinburgh.

Dr Tanya Melillo MD MSc(Dist) PhD is a public health consultant who heads the infectious disease prevention and control unit. Preparedness and response plans to new and emerging threats are part of the remit of this unit.

Dr Beatrice Farrugia MD is a specialist trainee in Public Health Medicine who is reading for her Masters in Public Health at the University of Malta. She is currently working at the Infectious Disease Control Unit.

ISSUE GUIDE

TheSynapse

SEROXAT®

The Anxiolytic Antidepressant:[1,2]

Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]

Panic Disorder[3]

Different indications require different dosage regimens. Please refer to the full SPC for more prescribing information.

SEROXAT ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: SEROXAT. **ACTIVE INGREDIENT:** Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20mg. **THERAPEUTIC INDICATIONS:** Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with and without agoraphobia, Social Anxiety Disorders/Social phobia, Generalised Anxiety Disorder, Post-traumatic Stress Disorder. **POSOLOGY AND METHOD OF ADMINISTRATION:** Administer once daily in the morning with food. Refer to full SPC for dosing information for specific conditions. Withdrawal symptoms seen on discontinuation of Paroxetine: abrupt discontinuation should be avoided. ***Elderly:*** maximum dose should not exceed 40mg daily. ***Children and adolescents:*** Should not be used. ***Renal/hepatic impairment:*** Dose should be restricted to lower end of dosage range. **CONTRAINDICATIONS:** Hypersensitivity. Should not be used in combination with MAOIs, thioridazine or pimozide. **PRECAUTIONS FOR USE:** Treatment to be initiated 2 weeks after terminating treatment with an irreversible MAOI or 24 hours with a reversible MAOI. Do not use in children and adolescents under the age of 18 years. Suicidal thoughts or clinical worsening: an improvement may not occur in the first few weeks of treatment. Akathisia. Serotonin syndrome/neuroleptic malignant syndrome may develop rarely: discontinue if such events occur. History of mania, renal and hepatic impairment, diabetes and in epilepsy, narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia, concomitant use with oral anticoagulants or drugs that increase risk of bleeding, history of bleeding disorders. Paroxetine may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen: concomitant use should be avoided. Withdrawal symptoms may occur on discontinuation of Paroxetine treatment. **DRUG INTERACTIONS:** Caution for use in combination with serotonergic drugs like St John's Wort, L-tryptophan, tramadol, linezolid, methylthioninium chloride, triptans, SSRIs, pethidine and lithium. Concomitant use with MAOI's is contraindicated. Caution with pimozide, anticonvulsants and with drugs metabolised by CYP 2D6. Reduced efficacy of tamoxifen. Caution in patients at an increased risk of bleeding and in patients on oral anticoagulants, NSAIDs, acetylsalicylic acid and antiplatelet agents. Adjust Seroxat dosage if necessary when given with drug metabolising enzyme inducers or with fosamprenavir/ritonavir. Concomitant use of alcohol is not advised. **PREGNANCY AND LACTATION:** ***Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated (*see full SPC for more detail*). ***Lactation:*** Use during lactation can be considered. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:** Patients should be cautioned about their ability to drive a car and operate machinery. **UNDESIRABLE EFFECTS:** ***Very Common (≥ 1/10):*** Nausea, Sexual dysfunction; ***Common (≥ 1/100, < 1/10):*** Increases in cholesterol levels, decreased appetite, somnolence, insomnia, agitation, abnormal dreams (including nightmares), dizziness, tremor, headache, blurred vision, impaired concentration, yawning, constipation, diarrhea, vomiting, dry mouth, sweating, asthenia, body weight gain. Increased risk of bone fractures in patients receiving SSRIs and TCAs. Common withdrawal symptoms include: dizziness, sensory disturbances, sleep disturbances, anxiety and headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. *Refer to full SPC for the full list of adverse reactions.* **LOCAL PRESENTATION:** Seroxat Tablets (by 30 tablets) **MARKETING AUTHORISATION HOLDER:** SmithKline Beecham Ltd. **MARKERTING AUTHORISATION NUMBERS:** MA172/00201. **DATE OF PREPARATION:** April 2015.

IN ORDER TO ENSURE THAT THIS PRODUCT INFORMATION REFLECTS THE MOST UP-TO-DATE CLINICAL AND POST-MARKETING SURVEILLANCE DATA, PLEASE ALWAYS REFER TO THE LATEST 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)**

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

Reference: 1. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH *et al.* Practice guideline for the treatment of patients with major depressive disorder (Third Edition) American Psychiatric Association 2010. 2. Baldwin *et al.* Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology Journal of Psychopharmacology 1–37 2014. 3. Seroxat SPC August 2015.

Job No: MLT_GIB/PXT/0003/16
Date of preparation: March 2016

UPDATE ON eHEALTH DEVELOPMENTS IN EUROPE

HUGO AGIUS MUSCAT

CROSS-BORDER EXCHANGE OF HEALTH RECORDS

The European Union (EU) has long aspired to support the freedom of movement of its citizens between member states by facilitating the transfer of their health records across borders. This is not as simple as might first seem, because few countries have a robust legal basis for such a transfer, records in different European countries are often in different languages, and the structure of health records varies greatly from country to country. At present most exchanges are informal and unstructured; hardly the best formula for safe and efficient healthcare.

Cross-border exchange of personal health data was first piloted during the epSOS (European Patient – Smart Open Services) project.[1] This was a large-scale pilot that ran from 2008 to 2014 and involved not only most EU countries but also Norway, Switzerland and Turkey. It focused on how to transfer patient summaries and ePrescriptions when citizens need unplanned health care while travelling outside their home country. Malta took part from 2011 onwards, and succeeded in exchanging patient summaries with various countries, including Italy, Portugal and Slovenia. The epSOS project drew up specifications for other use cases, such as transfer of a health care encounter report back to the patient's home country, and direct patient access to the cross-border data. However, these use cases have not been widely tested yet.

The European Commission is now encouraging countries to set up cross-border health data exchange as a routine service, and is supporting this by making funds available from its Connecting Europe Facility (CEF).[2] A call for applications opened in November 2015, inviting proposals from EU member states interested in connecting to the EU's new eHealth Digital Service Infrastructure (DSI). The call closed in March 2016 (CEF-TC-2015-2);[3] twenty countries submitted a proposal, and it is expected that the eHealth DSI will go live in the first quarter of 2018.

In parallel, the EU has been actively cooperating with the US in the specification and testing of an International Patient Summary standard that draws upon EU epSOS and the US Meaningful Use experience.[4]

e-SENS (ELECTRONIC SIMPLE EUROPEAN NETWORKED SERVICES)[5]

The European Commission is keen on integrating the outputs of various projects into its Digital Service Infrastructures. One of these projects is e-SENS, which included an eHealth component that focused on using European e-ID services to improve access to eHealth services. The aim is to help EU citizens not just identify themselves when accessing health services, but also demonstrate their entitlement to care and facilitate access to their cross-border health records in real time. Estonia and the Netherlands are the first countries testing the e-SENS online processes which allow the checking of health insurance entitlements of visiting citizens in real time by communicating with that citizen's own member state.

MOBILE HEALTH (mHEALTH) APPLICATIONS

In the past few years, the increasingly widespread possession of smartphones has led to a veritable explosion in the number of mobile apps available to the man in the street. More than 100,000 of these are related to health and lifestyle. A more recent trend is the increase in wearable devices, especially smartphones and fitness bracelets; this has further fuelled interest in mHealth. Jurisdictions around the world are trying to keep up with this rapid evolution. The challenge is to reap the benefits without losing sight of crucial factors such as safety, privacy and efficacy.

In April 2014, the European Commission issued a Green Paper on mobile health (mHealth) to help identify the right way forward to unlock the potential of mHealth in the EU. The summary report of the consultation, issued in January 2015,[6] makes for interesting reading; it addresses points such as the need for certification in order to generate trust in specific mHealth apps, and the role of standards in the generation of "big data" from such apps.

More recently, the European Commission has facilitated the creation of an industry-led **Code of Conduct** on mobile health apps, covering the topics of privacy and security. The objective is to foster citizens' trust in mHealth apps and to raise awareness of and facilitate compliance with EU data protection rules for

app developers. It covers issues such as user consent, purpose limitation, data retention, disclosure of data to third parties and data gathered from children. The Draft of this Code was published on 7 June 2016,[7] and it is now being looked at by the Article 29 Working Party on data protection.

Another recent EU policy initiative is the preparation of **mHealth app assessment guidelines**. In February 2016, the European Commission appointed a working group to draft these guidelines. The group includes representatives of patients, health professionals and providers, payers, industry, academia and public authorities. The group is seeking to provide common quality criteria and assessment methodologies that could help different stakeholders, in particular end-users, to assess the validity and reliability of mobile health applications. The guidelines are expected to build on existing initiatives and best practices in Europe. The latest draft may be downloaded from the dedicated web page.[8]

RESEARCH AND INNOVATION IN eHEALTH

Through its Horizon 2020[9] Programme, the EU provides substantial funding for research and innovation projects in the field of ICT for health and wellbeing. A few examples of such projects[10] are:

- A Decision Support System incorporating a validated patient-specific, multi-scale Balance Hypermodel towards early diagnostic Evaluation and efficient Management plan formulation of Balance Disorders (EMBalance)
- Clinical Intervention Modelling, Planning and Proof for Ablation Cancer Treatment (ClinicIMPPACT)
- Wearable Sensing and Smart Cloud Computing for Integrated Care to COPD Patients with Co-morbidities (WELCOME).

New research & innovation actions that will open in November 2016 and close in March 2017 include "In-silico trials for developing and accessing biomedical products" (SC1-PM-16-2017) and "Personalised computer models and in-silico systems for well-being" (SC1-PM-17-2017).[11]

eHEALTH WEEK IN MALTA: MAY 2017

From Tuesday 9th to Friday 12th May 2017, a series of eHealth events known collectively as "eHealth Week"[12] will be jointly organised and hosted in Malta by the Maltese Presidency, the European Commission and HIMSS-Europe.[13] eHealth Week is an annual gathering of the top eHealth policy makers and practitioners in Europe. It is estimated that around 2,000 delegates will attend from Europe and beyond.

These events will be held in Malta because, since 2007, the EU member state holding the first-semester Council Presidency and the European Commission have hosted a High-Level eHealth Conference. Almost every year since 2010, this has been co-located with a Health IT conference and exhibition organised by HIMSS-Europe, the European branch of HIMSS, a global not-for-profit organization focused on better health through IT. Since 2012 the European Commission has also organised a meeting of its eHealth Network alongside these conferences.

The main conference and exhibition will be spread over the three days from 10th to 12th May. It will include daily plenaries and parallel education sessions covering several themes. A particular feature is the SME Competition organised by the European Commission, which aims to recognise and reward SMEs that are leaders in the development of health IT applications. HIMSS also organises "matchmaking" sessions, which are opportunities for health IT companies, health providers and other stakeholders to meet.

Since January 2016, the Ministry for Health has been working on the thematic content of the Conference. It is planned to take forward discussions on the following themes:

- Giving patients direct access to their own data;
- Using data for personalised medicine, health technology assessment and analytics;
- Moving personal health data across borders (even for migrants);
- Supporting European Reference Networks[14] through eHealth;
- Joining up patient data from different sources;
- Improving safety and privacy of mobile health;
- Moving health data safely onto cloud infrastructure.

Visitors will be able to see Malta's eHealth systems in action, including the new version of the myHealth portal and other local Health IT deployments. A central theme in eHealth Week 2017 will be how to keep IT at the service of patients, citizens and society in general.

eHealth Week 2017 will be a golden opportunity for local healthcare providers and health IT companies to network with health IT leaders from all across Europe. For more information on this series of events, or on other eHealth matters, readers are encouraged to contact the Ministry for Health's Information Management Unit on digitalhealth@gov.mt.

1. www.epsos.eu/
2. ec.europa.eu/digital-single-market/en/connecting-europe-facility
3. ec.europa.eu/inea/en/connecting-europe-facility/cef-telecom/apply-funding/2015-cef-telecom-call-ehealth-2015-cef-tc-2015
4. ec.europa.eu/digital-single-market/en/news/trillium-bridge-recommends-international-patient-summary-standard
5. esens.eu/
6. ec.europa.eu/digital-single-market/en/news/summary-report-public-consultation-green-paper-mobile-health
7. ec.europa.eu/digital-single-market/en/news/code-conduct-privacy-mhealth-apps-has-been-finalised
8. ec.europa.eu/digital-single-market/en/news/current-initiatives-unlock-potential-mobile-health-europe
9. ec.europa.eu/programmes/horizon2020/
10. ec.europa.eu/digital-single-market/en/programme-and-projects/project-factsheets-ehealth
11. ec.europa.eu/digital-single-market/en/news/funding-ehealth-projects-new-horizon-2020-work-programme-2016-2017
12. ehealthweek.org/
13. himss.eu/
14. ec.europa.eu/health/ern/policy/index_en.htm

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

COPD

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

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

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

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

Please refer to the full Summary of Product Characteristics before prescribing

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

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

REPORTING ADVERSE EVENTS (AEs):

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

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

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

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

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

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

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

gsk

Theravance

OTOMIZE

Neomycin sulfate 0.5%w/w
Dexamethasone 0.1% w/w
Glacial Acetic acid 2.0% w/w
5mL bottle

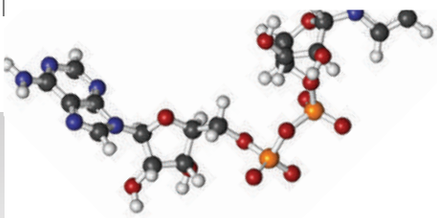
For the treatment of Otitis Externa

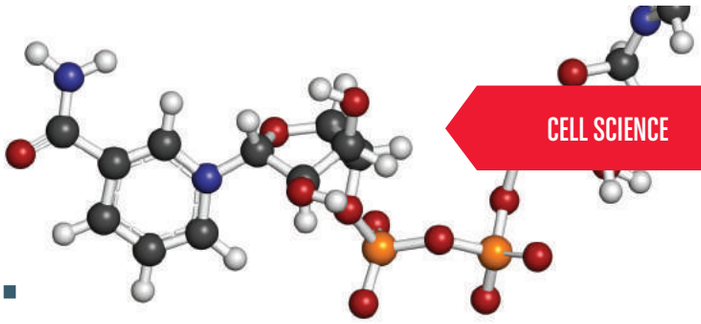
Abridged Prescribing Information: *Please refer to Full Summary of Product Characteristics before prescribing.***Name of Medicinal Product:** Otomize. **Composition:** Neomycin Sulfate. 0.5% w/w (3250 IU/ml), Dexamethasone 0.1% w/w, Glacial Acetic Acid 2.0% w/w. Contains methyl and propyl hydroxybenzoates (E218 and E216) which may cause allergic reactions (possibly delayed). Contains stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis). **Pharmaceutical form:** A milky oil-in-water emulsion as a liquid ear spray for application into the external auditory meatus. **Indications:** For the treatment of otitis externa. **Posology and method of administration:** Adults, elderly & children 2 years of age and over: One metered dose (60mg) administered directly into each affected ear three times daily. Treatment should be continued until two days after symptoms have disappeared. Otomize ear spray is not suitable for infants and neonates (under 2 years of age). **Instructions for use/handling:** Shake the bottle well before use. Before first use, press actuator down several times to obtain a fine spray. Each press then delivers one metered dose. Do not inhale the spray. Administer spray directly by gently placing nozzle tip into ear opening and pressing down once on the actuator. Use within one month of first use. If there is a period of more than one week since last use, press actuator down a few times before using again. **Contraindications:** Hypersensitivity to any of the ingredients. The product should not be used in patients where a perforated tympanic membrane has been diagnosed or is suspected or where a tympanostomy tube (grommet) is in situ. **Special warnings and precautions for use:** Discontinue treatment and seek medical advise if there is no clinical improvement after 7 days or if irritation or rash occurs, Exclude other chronic alternate diagnoses, including chronic otitis media, before treatment is commenced. Treatment with corticosteroid/antibiotic combinations should not be continued for more than 7 days in the absence of any clinical improvement, since prolonged use may lead to occult extension of infections due to the masking effect of the steroid. In children there is a theoretical risk that sufficient steroid may be absorbed to cause adrenal suppression, with prolonged use increasing this risk of adrenal suppression in children. Prolonged use may also lead to skin sensitisation and the emergence of resistant organisms. Due to potentially immature renal function in children toxicity may develop, thus caution is warranted when administering neomycin in this age group. Aminoglycoside antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. This possibility should be considered when high doses or prolonged treatment is given to small children. **Pregnancy and lactation:** Otomize is not recommended during pregnancy. **Lactation:** A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Otomize therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Effects on ability to drive and use machines:** Unresolved ear problems could themselves affect driving ability. **Undesirable effects** Some patients may experience a transient stinging or burning sensation for the first few days of treatment. Skin sensitisation / hypersensitivity reactions (immediate and delayed) leading to irritation, burning, stinging, itching and dermatitis. **Marketing Authorisation Holder:** Forest Laboratories UK, Limited, Whiddon Valley, Barnstaple, North Devon, EX32 8NS, United Kingdom. **Martketing Authorisation Number:** PL 00108/0332, AA003/0181. **Legal category:** POM. **Date of (partial) revision of the text:** 01/12/2015 Adverse events should be reported to the Malta Medicines Authority via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to phv@actavis.com.mt.

Always read the package insert. For further information please refer the Full Summary of Product Characteristics on **www.actavis.com.mt**

Actavis

ACT 06/2016 J4608





UPDATE ON SIRTUINS:
IS THERE ANY CLINICAL RELEVANCE?

ALFRED GRECH & MICHAEL BALZAN

ABSTRACT

Several studies have shown that the overexpression of sirtuins is associated with increased maximum lifespan in various model organisms, like the budding yeast *Saccharomyces cerevisiae*. Mammalian sirtuins were found to share homology with the yeast *Sir2,* causing gerontologists worldwide to wonder whether sirtuins could also influence ageing in humans. Increasing evidence suggests that sirtuins are implicated in cancer and metabolic, cardiovascular and neurodegenerative diseases.

INTRODUCTION

It has been over fifteen years since the Silent Information Regulator 2 (*Sir2*) gene was shown to extend the lifespan of the budding yeast *Saccharomyces cerevisiae.*[1,2] Since then, studies have been published showing that *Sir2* and its homologs, collectively known as sirtuins, are present in most organisms, including bacteria, plants and animals. In fact, they have been well conserved throughout evolution from archaebacteria to eukaryotes.[3] In evolutionary terms, conservation reflects functional significance, which is why gerontologists worldwide have been trying to understand how these sirtuins function at the cellular, molecular and organismal levels to alter mammalian physiology. For instance, discovering that they can perform nicotinamide adenine dinucleotide (NAD+)-dependent deacetylation reactions[4] opened up a new door of investigation into the metabolic control of sirtuins. Overall, it was shown that lifespan extension through the activation of sirtuins can be done either by calorific restriction or through pharmacological means. Theoretically, this, together with their wide range of activities, suggests that sirtuins could potentially be used as therapeutic targets to combat metabolic, neurodegenerative and age-associated human diseases.[5,6]

DISCUSSION

MAMMALIAN SIRTUINS AND THEIR CLINICAL RELEVANCE

Since *Sir2* was shown to enhance longevity in lower invertebrates, researchers started wondering whether sirtuins also influence ageing in mammals. In the latter, seven sirtuin proteins (SIRT1 to 7) were found to share homology with *Sir2.*[3] Of these, SIRT1 is the proto-member and the most commonly studied mammalian sirtuin. It modifies histones through deacetylation of lysine at position 26 in histone 1 (H1K26), K9 in histone H3 (H3K9) and K16 in histone H4 (H4K16). SIRT1 also deacetylates non-histone proteins that are involved in apoptosis, calorie restriction, cell growth, cell senescence, neuronal protection, organ metabolism and function, and tumourigenesis. In this review, most of the examples will be given on SIRT1 and its involvement in age-related diseases such as **cancer, metabolic**, **cardiovascular** and **neurodegenerative diseases**. However, it is important to note that most of the mammalian sirtuins are involved in a broad range of processes, including ageing, apoptosis, circadian clocks, energy responses to low calorie availability, inflammation, mitochondrial biogenesis, and stress resistance.

Roles of Sirtuins in Cancer and Metabolic Disorders:

Most cancers are characterised by **genomic instability** and **altered metabolism**. Metabolic reprogramming is involved in the response to cellular DNA damage. Therefore, defining the molecules that tune metabolism in response to DNA damage would help to better understand the mechanisms of carcinogenesis. Several studies suggest that the best characterised sirtuin, SIRT1, is a tumour suppressor which improves genomic stability.

However, controversy regarding the role of SIRT1 in cancer exists, since it appears to be bifunctional, operating both as a tumour suppressor and as a tumour promoter, depending on the context and its targets in specific cancers or specific signalling pathways. Evidence for SIRT1's promotion of tumour development and progression revolves around its function as a deacetylase where it acts to suppress the functions of tumour suppressors such as p53. Silencing of these tumour suppressors then prevents cell senescence and DNA damage-induced apoptosis from occurring, therefore allowing cells to proliferate and survive. On the other hand, SIRT1 may also act by suppressing tumour growth; this it does by suppressing NF-κB, a transcription factor with a role in the regulation of tumourigenesis, the dysregulation of which leads to tumour malignancy.[7]

Setting this controversy aside, the roles of sirtuins in maintaining genomic stability have been described as regulators of DNA repair pathways. Oberdoerffer *et al.*,[8] for instance, showed that in response to DNA damage, SIRT1 is recruited to DNA double strand breaks (DSBs); this recruitment is essential for the accumulation of DNA damage response proteins such as BRCA1, NBS1 and Rad51. BRCA mutations are the main known hereditary factors for ovarian cancer. Recently, Li *et al.*[9] highlighted crosstalk between BRCA1 and SIRT1 which may be beneficial for the balance between processes related to BRCA1 and SIRT1-related energy metabolism and stress responses. In addition, when DNA DSBs occur, SIRT1 promotes DNA repair by deacetylating WRN, a helicase important in maintaining genomic stability. SIRT1 is also involved in non-homologous end joining DNA repair. Upon UV damage, a different repair mechanism is involved, specifically, the nucleotide excision repair (NER) mechanism. SIRT1 can regulate

NER by deacetylating and activating xeroderma pigmentosum A and C proteins. When deacetylated, these proteins recognise single stranded DNA binding proteins and recruit other NER factors at the breaks so as to initiate DNA repair.[10] Seeing how sirtuins possess dual roles in DNA repair and metabolism, they can serve as central points in regulating both processes. Indeed, a recent realisation is that DNA damage can trigger metabolic responses, therefore indicating that these two biological entities may function in a coordinated fashion.

It is because of their dependency on NAD+ that sirtuins are thought to play a regulatory role in metabolic pathways. Given its involvement in adipogenesis, fat mobilisation, gluconeogenesis, glycolysis and insulin secretion, SIRT1 has also been implicated in calorie restriction and in insulin resistance at different metabolic tissues. Chen *et al.*[11] showed that mice lacking SIRT1 fail to show increased activity in response to calorie restriction. Recent data has also indicated that the activation of SIRT1 improves the insulin sensitivity of adipose tissues, liver and skeletal muscle, and that it also protects the cell mass and function of pancreatic beta-cells. Such findings point towards SIRT1 as a potential therapeutic target for the prevention of diseases such as metabolic syndrome and type 2 diabetes mellitus.[12]

Roles of Sirtuins in Cardiovascular Diseases:

SIRT1-4 were found to regulate the activities of several coregulators, enzymes and transcription factors that improve metabolic control in adipose tissue, liver, pancreas and skeletal muscle, especially during ageing and obesity. Through the deacetylation of forkhead box O1 (FoxO1) and p53, SIRT1 and SIRT7 have the ability to control myocardial development, and also, resist myocardial dysfunction associated with ageing and stress. In addition, by regulating the expression of angiotensin II type 1 receptor, and the activity of FoxO1, endothelial nitric oxide synthase and p53, SIRT1 can promote regenerative and vasodilatory functions, particularly in the endothelial and smooth muscle cells of the vascular wall. SIRT3 protects cardiomyocytes from ageing and oxidative stress, and together with SIRT6, it also acts to attenuate cardiac hypertrophy. SIRT7 was found to regulate apoptosis and stress responses in the heart.[13] Given that the activation of sirtuins has such a potentially beneficial effect on cardiovascular health, the interest in developing specific sirtuin agonists is corroborated. Moreover, because their activity depends on the availability of NAD+, enzymes involved in the biosynthesis of NAD+, including nicotinamide phosphoribosyltransferase, may also be valuable targets for the management of cardiovascular disease.

Roles of Sirtuins in Neurodegenerative Diseases:

SIRT1 and SIRT2 have been found to be associated with age-associated brain disorders. In animal models, overexpression of SIRT1 protects against amyloid-beta plaque formation. Overexpression of SIRT1 was also shown to suppress the formation of alpha-synuclein aggregates, a characteristic of pathological conditions such as Parkinson's disease and dementia with Lewy bodies.[14] Knocking out SIRT1 in a mouse model of Huntington's disease aggravated the pathology of the brain, whereas its overexpression improved survival and neuropathology.[15] Due to its ability to deacetylate FOXO3, SIRT2 was found to increase the expression of the antioxidant mitochondrial superoxide dismutase. It is widely accepted that oxidative stress is connected to neurodegenerative diseases.[16]

Sirtuin-Activating Compounds (STACs):

STACs are molecules that potentially can be used for the treatment of ageing and age-associated diseases.[17,18] Studies have indicated that both natural and synthetic STACs work to stimulate the activity of sirtuins. Resveratrol, a SIRT1 activator, is perhaps the most eminent STAC. Companies, such as Sirtris Pharmaceuticals, Inc., used to develop STACs, with its lead candidates being SRT2104 and SRT2379, both of which are potent activators of SIRT1. However, controversies behind this 'longevity' company led to its shutdown.

CONCLUSION

Sirtuins affect many biological substrates and the identification of the molecular players involved and their networks is still under intensive research. Surely, when the safety and efficacy of sirtuin modulators have been worked out, they will eventually find their place in the treatment of age-associated diseases.

REFERENCES

1. Sinclair DA, Guarente L. Extrachromosomal rDNA circles - A cause of aging in yeast. Cell. 1997;91(7):1033-42.
2. Kaeberlein M, McVey M, Guarente L. The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. Gene Dev. 1999;13(19):2570-80.
3. Frye RA. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. Biochem Bioph Res Co. 2000;273(2):793-8.
4. Imai S, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature. 2000;403(6771):795-800.
5. Westphal CH, Dipp MA, Guarente L. A therapeutic role for sirtuins in diseases of aging? Trends Biochem Sci. 2007;32(12):555-60.
6. Haigis MC, Sinclair DA. Mammalian Sirtuins: Biological Insights and Disease Relevance. Annu Rev Pathol-Mech. 2010;5:253-95.
7. Lin Z, Fang D. The Roles of SIRT1 in Cancer. Genes & cancer. 2013;4(3-4):97-104.
8. Oberdoerffer P, Michan S, Mcvay M, Mostoslavsky R, Vann J, Park SK, et al. SIRT1 Redistribution on Chromatin Promotes Genomic Stability but Alters Gene Expression during Aging. Cell. 2008;135(5):907-18.
9. Li D, Bi FF, Chen NN, Cao JM, Sun WP, Zhou YM, et al. A novel crosstalk between BRCA1 and sirtuin 1 in ovarian cancer. Sci Rep-Uk. 2014;4.
10. Fan W, Luo JY. SIRT1 Regulates UV-Induced DNA Repair through Deacetylating XPA. Mol Cell. 2010;39(2):247-58.
11. Chen D, Steele AD, Lindquist S, Guarente L. Increase in activity during calorie restriction requires Sirt1. Science. 2005;310(5754):1641-.
12. Cao Y, Jiang X, Ma H, Wang Y, Xue P, Liu Y. SIRT1 and insulin resistance. Journal of diabetes and its complications. 2015.
13. Borradaile NM, Pickering JG. NAD(+), sirtuins, and cardiovascular disease. Current pharmaceutical design. 2009;15(1):110-7.
14. Donmez G, Outeiro TF. SIRT1 and SIRT2: emerging targets in neurodegeneration. Embo Mol Med. 2013;5(3):344-52.
15. Jeong H, Cohen DE, Cui L, Supinski A, Savas JN, Mazzulli JR, et al. Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway. Nature medicine. 2012;18(1):159-65.
16. Wang F, Nguyen M, Qin FXF, Tong Q. SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. Aging Cell. 2007;6(4):505-14.
17. Gan L. Therapeutic potential of sirtuin-activating compounds in Alzheimer's disease. Drug news & perspectives. 2007;20(4):233-9.
18. Hubbard BP, Sinclair DA. Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends Pharmacol Sci. 2014;35(3):146-54.

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

Actifed*

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

Actifed* DM COUGH LINCTUS

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

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

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

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

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

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

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

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

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

ZIKA VIRUS: A GLOBAL HEALTH THREAT

BEATRICE FARRUGIA & TANYA MELILLO

ABSTRACT

The ongoing outbreak of Zika virus has captured media attention and caused worldwide concern. This article highlights the typical clinical picture and possible complications of this disease, current recommendations for personal protection and prevention, its implications for couples of child-bearing age as well as the local situation with regards to Zika virus.

INTRODUCTION

Zika is a mosquito-borne Flavivirus which is transmitted to humans through the bite of infected mosquitoes from the *Aedes* genus. It was first discovered in 1941 and has since caused sporadic disease in Africa and Asia. Zika recently caught the media's attention following an outbreak that started in Brazil in May 2015.[1] It was during this outbreak that Zika virus was linked to an increased incidence of the birth defect known as microcephaly, which results in babies born with abnormally small heads and central nervous system malformations. Zika was confirmed as a threat to pregnant women after laboratory research demonstrated its detrimental effects on developing nerve cells in foetuses.[2] It has also been linked to Guillian Barré syndrome.[3]

Since the start of the 2015 outbreak this virus has spread geographically to Latin America, the Caribbean and parts of Oceania. Currently, 61 countries and territories are experiencing ongoing Zika transmission while over seven hundred cases of travel-associated Zika have been reported in a total of ten EU countries since May 2015.[4] On 1st February 2016, the World Health Organisation declared Zika virus a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (2005)[5] due to emerging data linking this virus to transplacental infections, adverse foetal outcomes, congenital CNS malformations and neurological complications as mentioned above.[6]

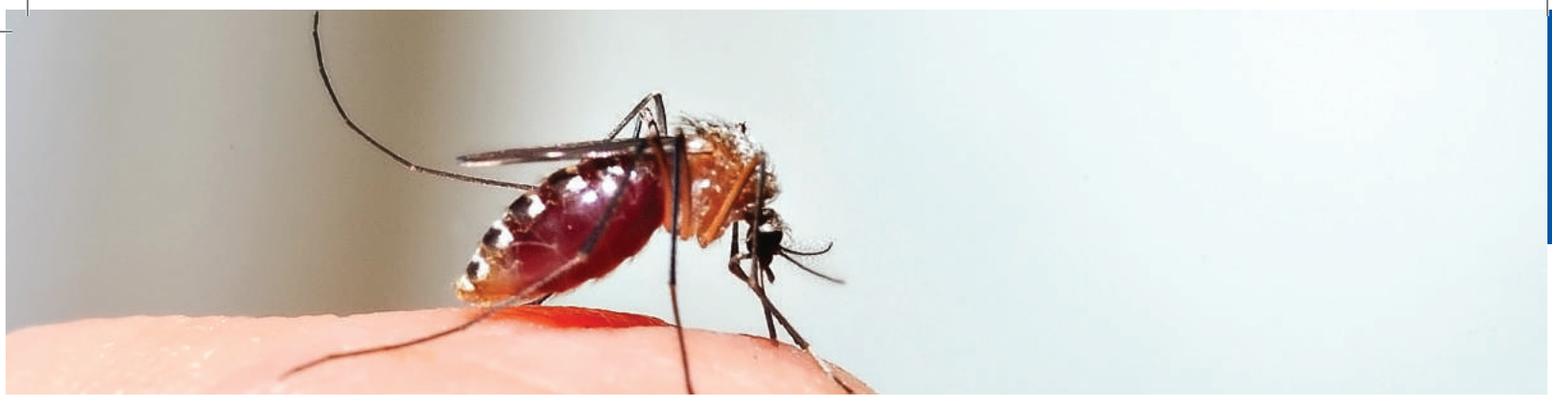
CLINICAL FEATURES

The incubation period for Zika virus is 3 to 7 days, with only 20% of those infected going on to develop clinical symptoms.[7] The symptoms of Zika virus are similar to those caused by other arboviruses such as Dengue and Chikungunya, and include low-grade fever, maculopapular rash, conjunctivitis, fatigue, myalgia and arthralgia.[6] The symptom most characteristic of Zika virus infection is maculopapular rash.[6] Symptoms usually last 7-10 days and are mild, self-limiting and non-specific. Zika virus is known to be detectable for at least 7 days after development of symptoms in blood, at least two weeks in urine and at least 2 months in semen.[8] It has also recently been detected in vaginal secretions.[9] Diagnosis is carried out using RT-PCR techniques.

MODE OF TRANSMISSION

Zika is a vector-borne disease which is most commonly transmitted via the bite of an infected *Aedes Aegypti* mosquito. However, studies have shown that *Aedes Albopictus*, commonly known as the Asian Tiger mosquito, can also transmit this virus. Other modes of transmission include:

1. Vertical transmission from mother to child during pregnancy or childbirth;
2. Transmission via blood transfusion;
3. Transmission from a sexual partner.



The latest information regarding sexual transmission of Zika virus is based on a recent report documenting a case of female-to-male Zika virus transmission and confirming the detection of Zika RNA in vaginal secretions.[10] Male-to-female and male-to-male transmission has been already documented. This recent discovery implies that any type of sexual activity (be it vaginal, anal, oral, or contact with genital secretions) can lead to Zika exposure in sexual partners of both male and female individuals who are infected with Zika virus. All those who can potentially be infected with Zika (males and females) are advised to consistently and correctly use male or female condoms for vaginal and anal sex. Attention should be paid when sharing sex toys. Appropriate barriers should also be used for oral sex.[11]

WHO now recommends that travellers to Zika-affected countries should delay conception and abstain from sex or practice safe sex for a period of at least eight weeks after their return if they do not develop any symptoms suggestive of Zika virus infection. Individuals who do develop symptoms compatible with Zika virus infection or for whom Zika infection has been confirmed by laboratory testing should delay conception and abstain or practice safer sex for six months after recovery.[12] Pregnant women with male or female sex partners who live in or have travelled to a Zika-affected country are advised to abstain from sex or consistently practice safer sex for the duration of the pregnancy.[9]

PREVENTIVE MEASURES

There is no existing licensed vaccine or specific treatment for the Zika virus available. However, research into vaccine development is ongoing. A DNA plasmid vaccine known as GLS-5700 was granted US Food and Drug Administration approval for a Phase 1 safety trial in human volunteers in June, while another two candidate vaccines have shown promising results in mice.[13] Preventive measures centre on personal protection from mosquito bites, avoiding pregnancy while in Zika-affected areas and postponing travel to these areas if pregnant. Travellers returning from Zika-affected countries are deferred from donating blood at the National Blood Transfusion Service for a period of four weeks.

The following advice is taken from the Infectious Disease Control Unit's publication: 'Information for People Travelling to Zika-affected areas' and relates to personal protective measures against mosquito bites.[14]

1. Protect skin from exposure to mosquitoes by wearing long sleeves, long trousers and hats.
2. Use mosquito repellent that has DEET as an ingredient (30-50% concentration for those above 2 years of age including pregnant women, 20% concentration for children under 2 years). Repellents may be applied to exposed skin or to clothing. Repellents are safe to use during pregnancy and in infants older than 3 months. Repellents need to be applied at regular intervals and must be used in strict accordance with the instructions indicated on the product label, especially regarding duration of protection and frequency of reapplication. If a traveller is applying both sunscreen and insect repellent, the sun screen should be applied first, followed by the insect repellent.
3. Use physical barriers such as mosquito screens on doors and windows.
4. Sleep in closed air-conditioned accommodation or under insecticide-treated mosquito netting especially when resting during the day, when Aedes mosquitoes are most active.
5. Eliminate any possible mosquito breeding sites, such as standing collections of water while staying in a Zika-affected country.

THE LOCAL SITUATION

Aedes albopictus (Asian Tiger mosquito), a potential vector for Zika virus, is known to be present on the Maltese Islands.[15] There is, however, no evidence to suggest that our local mosquito population is infected with Zika virus.[16] The public health authorities are preparing a national plan on mosquito-borne diseases and surveillance of mosquitoes is being enacted.

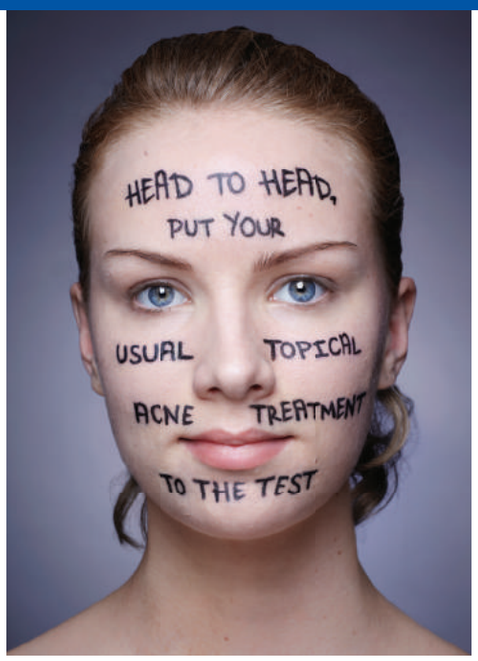
Zika has recently been declared a notifiable disease in Malta together with Dengue, Chikungunya and West Nile fever.[17] Testing for all these vector-borne diseases is now possible locally. Symptomatic returning travellers are obliged to contact public health authorities no later than the day after their return so that the necessary precautions are taken and testing is carried out.

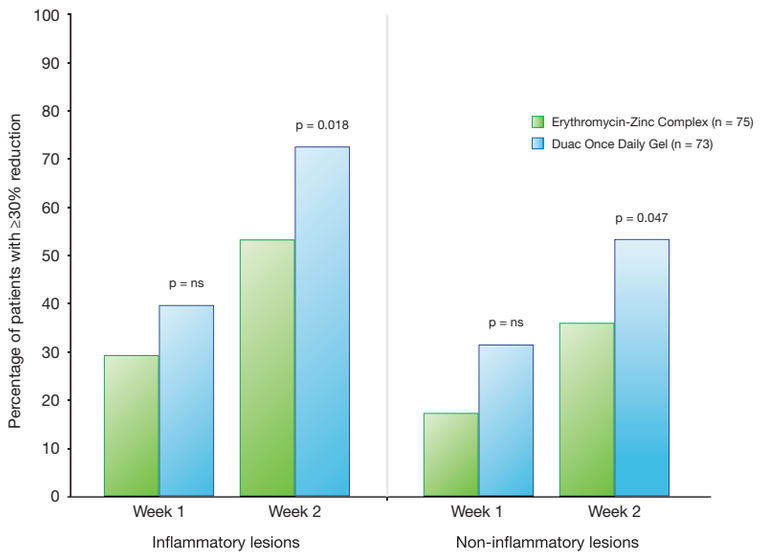
An awareness campaign is also being carried out with the general public. This includes social media updates, information leaflets and posters encouraging individuals to contribute to vector control. Posters have also been set up at the airport and seaport with information for outgoing and returning travellers. Detailed advice for travellers to Zika-affected areas and travellers to the Rio Olympics, as well as further information on Zika virus, is available on the Infectious Disease Prevention and Control Unit's (IDCU) website. Those requiring further information can contact the Zika helpline on 21324086.

IDCU website link: http://health.gov.mt/en/health-promotion/idpcu/Pages/introduction.aspx

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX[1]





Graphs adapted from Langner A *et al. JEADV* 2007

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex[1]
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks[1]
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[4]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[3]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

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

TIPS[3]

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

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

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

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

Local Presentation: 30g gel. **Marketing Authorization Holder:** GlaxoSmithKline UK Ltd., Trading as Stiefel. **Marketing Authorization Number:** MA 300/01401. **Legal Category:** POM.

Date of Preparation: January 2016

IN ORDER TO ENSURE THAT THIS PRODUCT INFORMATION REFLECTS THE MOST UP-TO-DATE CLINICAL AND POST-MARKETING SURVEILLANCE DATA, PLEASE ALWAYS REFER TO THE LATEST SPC, WHICH IS AVAILABLE FROM: GSK (MALTA) LIMITED (TEL: 21238131)

REPORTING ADVERSE EVENTS (AEs):

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

Malta: **alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

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

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

Stiefel
a GSK company

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

Job no.: MLT_GIB/CBP/0001/15 Date of preparation: January 2016

GALVUS and EUCREAS

COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

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

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

Galvus®
PRESENTATION: Each tablet contains 50 mg of Vildagliptin. INDICATIONS: For the treatment of type 2 diabetes mellitus in adults: As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin, a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a 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 ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class III treated with Vildagliptin is still limited and results are inconclusive. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving Vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. Use of Vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Combination with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral, Uncommon: headache, asthenia, hypoglycaemia. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulence. Frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. **LEGAL CATEGORY:** POM **PACK SIZES:** 7, 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 003. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2015-MT- GAL-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 doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFTs should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema. Hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10): Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:**POM **PACK SIZES:** 30, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–003, EU/1/07/425/006-009. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872 2015-MT-EUC-16-DEC-2015

GAL Ad1 06/16 MT

NOVARTIS

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

Galvus® vildagliptin

Eucreas® vildagliptin/metformin

TYPE 2 DIABETES MELLITUS IN MALTA

KIRSTEN SCHEMBRI

ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a major health problem in Malta. Prevention strategies should focus on patient self-management skills, including a more active lifestyle and a balanced diet. The setting-up of a diabetes register would allow for a recall system leading to better follow-up and care of T2DM patients.

INTRODUCTION

According to data from the International Diabetes Federation (IDF), 10.1% of all 20-79 year olds in Malta suffer from T2DM.[1] Moreover, it is estimated that there are a further 12,000 undiagnosed diabetics in the Maltese population. Such data signifies the importance of devising strategies to prevent diabetes in order to control the morbidity and mortality which is brought about by its various complications. The most effective way to prevent the onset of diabetes is to work at the community level. This means that primary care has a crucial role in preventing this chronic condition. Patients suffering from diabetes should be empowered to be more responsible for the management of their condition. Psychosocial support for such patients and their families should also be reinforced. There should also be greater collaboration between healthcare professionals working in health centres, hospitals and in the private sector.

DISCUSSION

LEVELS OF PREVENTION

Strategies for preventing T2DM can be implemented at all the five different levels of prevention.

1. Primordial prevention entails prevention of the disease prior to the presence of a modifiable risk factor. In this case, one would, for instance, aim to maintain a healthy weight since being obese is a significant risk factor for T2DM.
2. Primary prevention[2] involves preventing the onset of disease in those patients who are at risk. Patients who have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) are at risk of developing T2DM and should be closely monitored in the community. IFG is defined by an elevated fasting plasma glucose (FPG) concentration (≥100 and <126 mg/dl), IGT is defined by an elevated 2-hour plasma glucose concentration (≥140 and <200 mg/dl) after a 75g oral glucose tolerance test (OGTT) in the presence of an FPG concentration <126 mg/dl.[3]
3. Secondary prevention involves the prevention of complications in those with established disease. This incorporates the prevention of diabetic neuropathy, retinopathy and nephropathy by regular assessment of such patients and referral for specialist care when appropriate.
4. Tertiary prevention entails reducing the risk of complications progressing further. For instance, a patient with background retinopathy should be followed-up in order to prevent the progression to pre-proliferative and proliferative retinopathy.
5. Quaternary prevention is an increasingly important theme in family medicine and refers to various means of rehabilitation and restoring function whilst preventing 'overmedicalisation', particularly in the elderly population.

Diabetes has a long preclinical phase ('prediabetes') which ranges from around 10 to 12 years. This provides an opportunity to exert effective preventive measures in order to delay the development of disease. Furthermore, individuals with undiagnosed diabetes who are experiencing symptoms (such as polyuria, polydipsia and weight loss) should be worked up immediately in order to limit the onset of comorbidities.

Unlike other diseases, the diagnosis of diabetes only requires a simple blood test, hence making the diagnostic process simple, cheap and convenient for both the clinician and the patient. Therefore, patients who present to their GP for a routine check-up should be encouraged to have their blood glucose tested regularly in order to establish their glycaemic status and address any problems when they are still in their infancy.

Several interventional studies[4,5] demonstrate that lifestyle interventions and weight loss can actually prevent the onset of T2DM. The Diabetes Prevention Programme (DPP) trial showed that moderate weight loss, dietary changes and physical activity reduced the likelihood of patients with prediabetes to progress to T2DM by 58%.

CURBING THE DIABETES EPIDEMIC IN THE COMMUNITY SETTING

Two main areas that should be targeted are an increase in physical exercise at a national level and dietary changes.[6] The IDF explicitly states that "Physical activity is one of the main pillars in the prevention of diabetes".[7] It also states that 30 minutes of exercise a day can reduce the risk of diabetes by 40%.[8]

In a study by Ekelund at al[9] it was shown that the health benefit of exercise is approximately double the expected health benefit arising from a reduction in obesity. Further to this, the UK Academy of Medicine studied the positive impact that regular physical activity could have on the nation's health. It was found

that 30 minutes of physical activity five times a week can actually prevent the onset of T2DM. In view of this, family physicians should be motivated to prescribe physical activity to their patients from early life to middle and old age.

Patients should also be actively encouraged by their family physician to follow certain simple rules with regards to a healthy balanced diet, such as:

- Including more whole grains (which are a good source of fibre) and lean sources of protein, particularly fish and vegetables;
- Avoiding white bread, white rice, mashed potatoes, processed meats, cakes and sweets;
- Avoiding products containing partially hydrogenated vegetable oils as found in margarines, packaged baked goods and fried foods. These should be substituted by polyunsaturated fats as found in liquid vegetable oils, nuts and seeds and, in particular, those found in fish;
- Avoiding breakfast cereals which contain sugar or which have a high glycaemic index. Soft beverages should be substituted by water, coffee or tea;
- Avoiding both active and passive smoking.

Above all, developing patient self-management skills is the way forward to effectively manage and care for diabetes. This means that doctors should empower their patients to learn about their condition and be able to independently control their blood glucose levels. This places patients at the centre of healthcare provision, as opposed to the paternalistic approach in which patients do not have an active role in managing their own conditions.

SCREENING

T2DM fulfils a number of criteria which makes it an excellent candidate for screening high risk populations. It has a large and growing disease burden, its natural history is well understood and there is a long asymptomatic pre-diabetic state. Screening for T2DM is low cost, safe and reliable. Such considerations are important in view of the fact that T2DM is a treatable disease and benefits from early treatment.

Earlier detection through screening policies represents a pivotal 'paradigm shift' for diabetes prevention.[10] Screening provides the entry point for T2DM prevention in patients with prediabetes, thus contributing to the avoidance of complications in previously undiagnosed patients with T2DM.

INFORMATION SYSTEMS FOR T2DM PATIENTS

A diabetes clinical information system has been in place for a number of years at the diabetes clinic since the 1990s, formerly at St Luke's Hospital and now at Mater Dei Hospital. This system forms part of a database building project, the European Shared Diabetes information system. It allows for online consultation with respective consultants at Mater Dei and advice on management is given without the need to refer patients for appointments.[11] However, this information system is not comprehensive since not all clinicians make use of the system and the system is not available to private family doctors. An ICT-based register of patients with diabetes would allow for integrated care between public hospitals and the community setting (health centres and the private sector). This would enable greater continuity of care amongst healthcare professionals and improve follow-up.

THE WAY FORWARD

T2DM is an ideal condition for screening. It is being proposed that, at least every two years, screening is carried out in health centres or in private clinics in those patients who have at least one of the following risk factors.

- Obese patients (BMI >=30 kg/m2) over 18 years of age;
- Overweight patients (BMI 25–29.9 kg/m2) between the age of 18 and 44 with a family history of diabetes;
- All patients above the age of 45;
- Adults with a systolic blood pressure greater than 130mmHg and/or cardiovascular disease;
- Previous occurrence of diabetes in pregnancy;
- Patients who are on medications that predispose to T2DM. Such drugs include nicotinic acid, glucocorticoids, thiazides, phenytoin and anti-psychotics.

CONCLUSION

The care given to T2DM patients should address the biological as well as the psychosocial aspects of the condition. Healthcare professionals caring for patients with diabetes should be trained to recognise signs and symptoms of psychological distress. Patients with poor social support should be appropriately referred to psychologists and social workers since social exclusion renders management of diabetes even more difficult. Holistic care can only be achieved when patients are cared for by a multidisciplinary team consisting of doctors, diabetes nurse specialists, dieticians, podiatrists and psychologists.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

astellas

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

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

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

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

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

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

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

REPORTING ADVERSE REACTIONS: If you become aware of any adverse reactions in association with the use of SEROXAT, please report the event promptly to:
GSK (Malta) Limited, 1, 1st floor, de la Cruz Avenue, Qormi QRM 2458, Malta or Tel. 21 238131.
Alternatively any suspected adverse reactions can also be reported to: Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: http://www.medicinesauthority.gov.mt/pub/adr.doc

Put depression behind them.

References: 1. Nutt DJ, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, *et al.* The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol 2007; 21: 461–471.

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

Wellbutrin® bupropion hydrochloride XR

The Noradrenaline & Dopamine Re-uptake Inhibitor.

CHOLESTEROL & STATINS
AN UPDATE

ALBERT CILIA-VINCENTI

The previous SYNAPSE series of articles on "The Cholesterol Controversy" discussed how the theory linking dietary saturated fat, blood cholesterol and atherosclerosis was established by an American biologist in the 1950s and how the concurrent claims of a London physiology professor, that sugar not fat was mainly responsible for atherosclerosis, were ignored. We also highlighted the evidence that sugars, refined carbohydrates, starches and trans-fatty acids raise blood triglycerides (TRGs) and lower HDL-cholesterol, and that this TRGs/HDL ratio (the higher above 1 the higher the risk) is a more accurate indicator of risk for atherosclerosis than any other blood lipid profile risk ratios in common use.

At the same time we learned of the recent doubts about the validity of LDL as a reliable marker for risk of atherosclerotic, based principally on the finding that what routine laboratories measure as "LDL" is in fact a mixture of two distinct sub-fractions of LDL, one is a large light particle and the other a small dense particle. The small dense particle is the one involved in atherosclerosis. Hence, when "LDL is raised" in routine lipid profiles, one doesn't know whether the innocuous large particle, or the dangerous small particle, is largely responsible for the "raised LDL". Prescribing statins for a raised innocuous large particle LDL would therefore be inappropriate. How does one get round this problem of routine laboratories measuring only one total LDL?

We learned that a raised TRGs/HDL ratio is a surrogate marker for the raised small dense particle LDL. We also know that a high refined carbohydrate, starchy and trans-fat diet, the metabolic syndrome, and diabetes, are characterised by a raised TRGs/HDL ratio. Their association with atherosclerosis risk thus becomes clearer.

The above doubts about the reliability of routine LDL measurements to assess atherosclerotic disease risk, combined with the lack of randomised controlled data relating to the effect of different intensities of statins or different combinations of medications on specific LDL levels, led the American College of Cardiology/American Heart Association to eliminate specific LDL targets from their 2013 cholesterol guidelines.[1]

However, the National Lipid Association (US),[2] the European Society of Cardiology[3] and the Canadian Cardiovascular Society[4] continue to include LDL targets, which adds to the confusion since these targets are not evidence-based. Interestingly, Alberico Catapano, president of European Atherosclerosis Society and professor of pharmacology at Milan University, advises looking at the TRGs (especially when high) when managing LDL.[5] Remember the above observation that a high TRGs/HDL ratio is a surrogate marker for high small dense particle (bad) LDL.

The pathological basis of atherosclerosis is now well established to be a chronic inflammatory arterial disease.[6] Current research concentrates on which inflammatory cytokines are pro- or anti-atherogenic, and which drugs may promote anti-atherogenic cytokines or which dampen the effects of pro-atherogenic ones. Anti-tumour necrosis factor alpha (TNFa) is one of the pro-atherogenic cytokines and anti-TNFa therapy is associated with a reduced risk for all cardiovascular events.[7]

The cardiovascular beneficial effect of statins have traditionally been associated with their hypolipidaemic effects but has also been shown to be due to their anti-inflammatory action mediated via modulation of cytokine action. High blood glucose increases TNFa levels and atorvastatin is known to lower the post-glucose loading levels of TNF-a.[8] This also indicates at least one mechanism via which elevated blood glucose promotes atherogenesis and, therefore, how a high refined carbohydrate and starchy diet is pro-atherogenic.

It has also been shown that reduction of C-reactive protein (CRP) levels with statin treatment is independent from the reduction of LDL levels.[9] Lovastatin has been shown to prevent cardiovascular events in those coronary artery disease subjects with especially high CRP despite a favourable LDL profile.[10] Another study demonstrated that in subjects with CRP levels higher than 2mg/L, even with low LDL levels, rosuvastatin can decrease cardiovascular events.[11]

As you would expect, in all this pharmaceutical company-funded research activity, there will be no randomised controlled trials comparing the claimed anti-inflammatory and anti-atherogenic potential of omega-3 fatty acids[12] with those of statins. Omega-3 fatty acids are of both marine and plant origin. The latter are probably not only safer but definitely cheaper (such as flaxseed oil capsules) than pharmaceutical grade fish oil (distilled to remove any possible heavy metal contamination).

TAKE-HOME POINTS

1. The little known fact that LDL has two sub-fractions, one "good" and one "bad", and that only one total LDL is routinely measured, questions the reliability of conventional LDL levels for adverse cardiovascular events risk assessment. It is hard to justify statin therapy when the TRGs/HDL ratio and the CRP level are within normal limits, irrespective of LDL level, particularly in primary prevention. The TRGs/HDL ratio and the CRP should be the two most important risk indicators.[13]
2. The pro-atherogenic effects of sugars, other refined carbohydrates, starches and trans-fats have been re-emphasised. Drug therapy without correct dietary and lifestyle advice does not constitute adequate management of cardiovascular health.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

THUASNE

Hand and Elbow

Ligaflex Classic Open

Light to moderate sprain
Wrist tendinitis with or without oedema
Carpal tunnel without surgery
Post-operative immobilization
Wrist injury

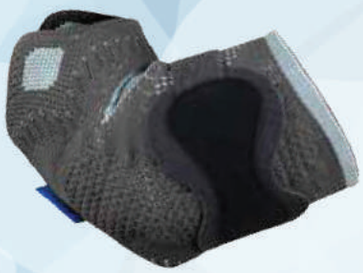
Ligaflex Rhizo

Thumb sprain and arthritis
Trapeziometacarpal

Jamesco Advert Rhizo-Pro

Thumb sprain

Silistab Epi



Tennis Elbow
Golfers Elbow
Treatment and precaution

JAMESCO
Trading Company Limited
A smarter approach to your health & wellbeing

Tel: 21314333

Doctor Strange is an upcoming American superhero film featuring the Marvel Comics character of the same name. It is intended to be the 14th movie of the Marvel Cinematic Universe (MCU). Various incarnations of Doctor Strange have been in development on the silver screen since the mid-1980s until Paramount Pictures acquired the film rights in April 2005 on behalf of Marvel Studios. It has been filmed in Nepal, UK, US and China. The plot revolves around Stephen Strange, the world's top neurosurgeon. After being injured in a car accident that ruins his career, he sets out on a journey of healing, where he encounters the Ancient One, who later becomes Strange's mentor in the mystic arts. Benedict Cumberbatch stars as Dr Strange. Cumberbatch is best known for his roles in the TV series *Sherlock*, and movies including *Star Trek Into Darkness* and *The Imitation Game*.

Directed By: Scott Derrickson
Produced By: Kevin Feige
Release Dates: October - November 2016

Source: marvel.com

MPSA

HEPATITIS

JESSICA ZARB

Hepatitis is an inflammation of the liver and can have different causes. Viral hepatitis is caused by five different types of viruses, type A to type E. However, types A, B and C are the most common. The prognosis includes liver cancer, cirrhosis, extreme fatigue, vertigo and jaundice.

Hepatitis A is transmitted via the faeco-oral route or through contaminated water or food. It does not lead to chronic long term liver disease.

Hepatitis B is transmitted via sexual contact, blood-to-blood contact such as infected needles and from mother-to-child during childbirth. It leads to chronic disease, usually liver cirrhosis and cancer. Symptoms include aches and pains, abdominal discomfort and hematuria. Once contracted 95% of adults will clear the virus and not develop chronic hepatitis B. There are two drug treatments, i.e. anti-viral medication, and peginterferon alfa or interferon alfa exhibiting immune-modulatory properties.

Hepatitis C is a blood-borne virus which is transmitted through infected needles or contaminated equipment. Although it is slow acting, it results in serious disease such as liver cancer.

Hepatitis D is transmitted through mucosal contact with infectious blood and can be acquired either as a co-infection with hepatitis B virus or as superinfection in people with hepatitis B virus infection. On the other hand, **hepatitis E,** like type A, is transmitted via the faeco-oral route.

As Desidius Erasmus said, *Prevention is better than cure*. Preventive measures are vital to combat these viruses. Vaccination is available against hepatitis A and B. Vaccines are not yet available for hepatitis C although some candidate vaccines are being studied. Sanitising hands and avoiding contaminated water are also essential at combating viral hepatitis.

THE REVISED ESC GUIDELINES ON HEART FAILURE – AN UPDATE

IN THIS INTERVIEW, COORDINATED BY DR IAN ELLUL, WE MEET DR ALICE MAY MOORE MD, MRCP(UK). DR MOORE IS CURRENTLY WORKING AT MATER DEI HOSPITAL AS A HIGHER SPECIALIST TRAINEE IN THE CARDIOLOGY DEPARTMENT. SHE HAS A SPECIAL INTEREST IN HEART FAILURE AND IN NOVEMBER 2016 SHE WILL BE EMBARKING ON A ONE YEAR TRAINING FELLOWSHIP IN THIS FIELD AT KING'S COLLEGE HOSPITAL, LONDON.

TS: **Heart failure is a common condition worldwide, steadily increasing in prevalence over time. One in five people over the age of 40 years will develop the condition in their lifetime. How common is heart failure in Malta?**

Heart failure is one of the commonest conditions in Malta. It affects around 1-2% of the whole population. That means that around 6000 Maltese people are estimated to be suffering from this condition.

TS: **At what stage of the condition do patients present, early or late? Does this affect the management and outcome?**

Heart failure is a clinical syndrome characterized by typical symptoms and signs caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output. Before clinical symptoms become apparent, patients can present with asymptomatic structural or functional cardiac abnormalities, which are precursors of heart failure. Recognition of these precursors is important because they are related to poor outcomes, and starting treatment at the precursor stage may reduce mortality in patients with asymptomatic systolic left ventricular dysfunction.

TS: **Worldwide, heart failure is the primary cause of hospitalization in patients aged >65 years. Is it the same in Malta? Is hospitalization due to heart failure a common cause of hospitalization in Malta? Do these patients require frequent re-hospitalization?**

Despite dramatic improvement in outcomes with medical therapy, re-hospitalization rates in Malta remain high. Heart failure is a complex deteriorating condition driven by neurohormonal imbalance, leading to a downward spiral of worsening disease and punctuated by acute episodes that result in repeated hospitalizations that lead to poor outcomes. The re-hospitalization rate at Mater Dei hospital between 2013-2014 was 29%.

TS: **What are we doing about heart failure in Malta? What do we offer patients? How does this help their prognosis?**

In an attempt to reduce the re-admission rate, a heart failure clinic was set-up at Mater Dei Hospital. Patients suffering from the disease visit this nurse-led clinic whenever required. The main priorities of the clinic are optimization of medical therapy (according to the recent guidelines) and education of the patient. The latter focuses mainly on the nature of the heart failure process by teaching patients about regular weighing and compliance with medical therapy and fluid restriction.

In 2015, a compassionate use programme was set-up in Malta with the novel heart failure drug Entresto® (sacubitril/valsartan). Nineteen patients who attend the heart failure clinic were initiated on this therapy. Most recorded an improvement in symptoms with a significant decrease in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels. NT-proBNP is a biological marker of acute congestive heart failure.

TS: **There were changes in the heart failure guidelines earlier this year. What has changed? What are your views on this? Is the treatment mentioned in the guidelines also available locally?**

The new European Society of Cardiology guidelines on Acute and Chronic Heart Failure[1] were presented in May 2016 in Florence at the Heart Failure Congress. Changes included a new classification and treatment algorithm. The new classification now includes: Heart failure with reduced ejection fraction (EF<40%); Heart failure with midrange ejection fraction (EF 40-49%); and Heart failure with preserved ejection fraction (EF >50%). The guidelines also indicate the use of the new compound Entresto® (sacubitril/valsartan), the first in the class of angiotensin receptor neprilysin inhibitors (ARNI): "In patients with chronic symptomatic HFrEF NHYA class II or III who tolerate an Angiotensin-converting enzyme inhibitor or Angiotensin II receptor blocker, replacement by an ARNI is recommended to further reduce morbidity and mortality" (Class I, Level of evidence B).

This novel heart failure therapy, which is now also available in Malta, proves to be very promising. The PARADIGM-HF study[2] showed that when Entresto® was compared to the conventional heart failure drug enalapril, there was a 20% risk reduction in death from cardiovascular causes and a 21% risk reduction in heart failure hospitalization.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
2. McMurray JJ, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.

ENTRESTO™ ▼(sacubitril/valsartan)
Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration:** The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended din patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. **B-type natriuretic peptide (BNP):** BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. **Interactions:** Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. **Fertility, pregnancy and lactation:** The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. **Undesirable effects:** Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes:** Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Frimley Business Park, Camberley, GU167SR, United Kingdom. **Marketing Authorisation Numbers:** Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. **Please refer to the Summary of Product Characteristics (SmPC) before prescribing.** Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2016-MT-ENT-16-JUN-2016

ACE = angiotensin-converting enzyme

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

NOVARTIS

ENT Ad1 08/16 MT

IMAGING THE CERVIX PART II

PIERRE VASSALLO

This article follows on Part I, which appeared in the last issue of The Synapse Journal. It will discuss imaging of endometriosis in the cervical canal and also cervical cancer. The importance of imaging in staging of cervical cancer will be stressed.

Endometriosis, a benign gynaecologic disorder that affects approximately 10% of women of reproductive age, is defined as endometrial tissue outside the uterus. Cervical involvement with endometriosis is rare occurring in 0.1%–2.4% of patients. Cervical endometriosis may be superficial or deep depending on the depth of penetration of the cervix. The pathogenesis of cervical endometriosis is unknown. Superficial cervical endometriosis may be an incidentally detected histologic finding in asymptomatic women. It may also manifest as a cervical mass, with symptoms of pelvic pain or abnormal vaginal bleeding. On ultrasound, cervical endometriosis may present as a complex cystic mass within the endocervical canal, but may even appear solid extending into the paracervical tissues. In the latter case, it could mimic leiomyomas, polyps, and even carcinoma. Although clinical history and speculum exam may suggest the diagnosis, biopsy confirmation is required.

Endometriosis usually presents through symptoms related to peritoneal infiltration, which may be superficial or deep (extending >5mm below the peritoneal surface). Deep infiltrating peritoneal lesions located in the Pouch of Douglas (Fig 1) may penetrate the posterior aspect of the cervix. External cervical penetration from an endometriotic lesion in the Pouch of Douglas would appear as a hypoechoic mass infiltration the posterior cervical stroma on ultrasound, and would mimic peritoneal carcinomatosis or invasive cervical cancer (Fig 2).

MR imaging may help to establish the correct diagnosis by showing the characteristic low T2 signal intensity resulting from haemosiderin deposition with high T1 signal foci representing fresh haemorrhage (Fig 3).

Cervical cancer is the leading gynecologic cancer worldwide. There are multiple known risk factors for development of cervical cancer, including history of multiple sexual partners, early age of first intercourse, multiparity, lower socioeconomic standing, cigarette smoking, immunosuppressed state, and use of oral contraceptives. There is also a strong association with human papillomavirus (serotypes 16, 18, 31, 33, and 56) accounting for more than 80% of all invasive cervical cancers. The increasing use of the human papillomavirus vaccine appears to be leading to a significant decrease in the incidence of cervical cancer.

The mucosal lining of the cervix is composed of columnar cells in its proximal portion and squamous epithelial cells more distally. The transition zone is the border that separates the proximal columnar lined cervical canal from the distal squamous cell lined portion. The transition zone lies more distally in younger women (20-40 years of age) and moves more proximally with increasing age. The transition zone is the site of development of cervical cancer. Thus cervical cancer tends to be closer to the external os and is more exophytic in younger women, while in older women it lies closer to the internal os and is more endophytic. 80-90% of cervical cancers are squamous cell cancers, while 5-20% (depending on published source) are adenocarcinomas.

Women with cervical cancer tend to present with abnormal vaginal bleeding mainly intermenstrual bleeding (metrorrhagia) and post-menopausal bleeding. Cervical cancer can also lead to cervical canal stenosis and obstruction resulting in hydrometra, haematometra and pyometra.

Accurate staging of cervical cancer is critical for proper management, because risk stratification and mode of treatment

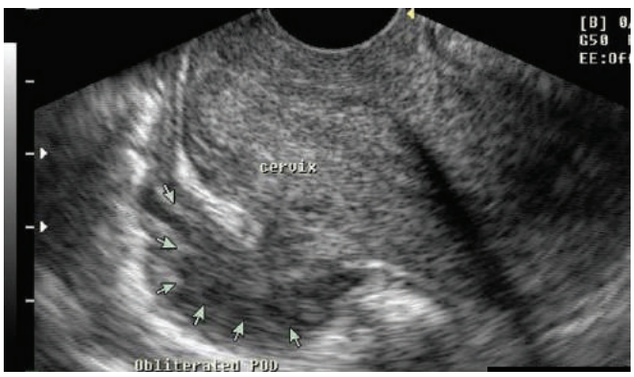


Figure 1. Sagittal endovaginal ultrasound in a case of endometriosis showing moderately echogenic nodule (arrows) with irregular margins lying posterior to the cervix and infiltrating/obliterating the Pouch of Douglas.

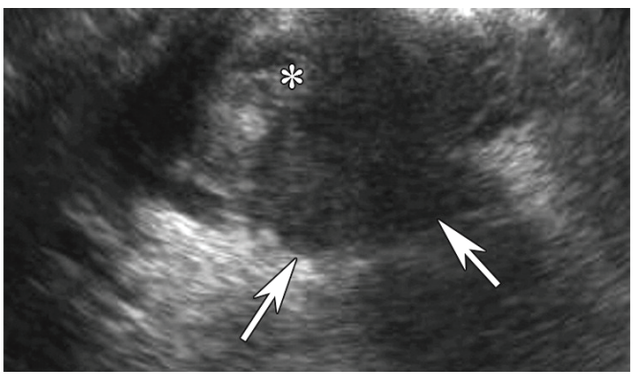


Figure 2. Coronal endovaginal ultrasound scan through the cervix in a case of endometriosis showing a hypoechoic mass centred in the Pouch of Douglas infiltrating the cervix posterolateral to the endocervical canal (*).

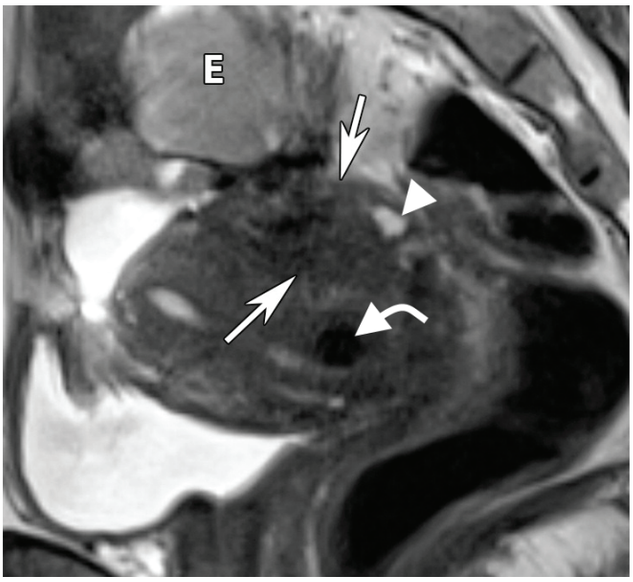


Figure 3. Sagittal T2-w MR image in a case of endometriosis showing an ill-defined mass (arrows) infiltrating the posterior wall of the uterus and cervix and the anterior wall of the rectum. The mass contains hypointense foci (curved arrow) due to haemosiderin content and hyperintense foci (arrowhead) due blood. A hyperintense mass (E) seen superior to the uterus represents an endometrioma.

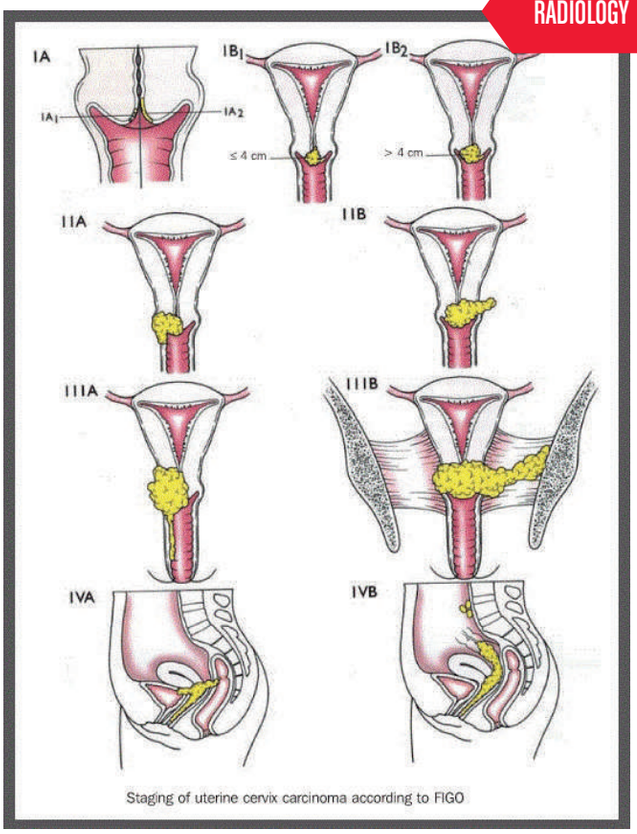


Figure 4. FIGO staging of cervical cancer.

depend on tumour size, the presence and extent of local invasion and the presence of metastases. Traditionally, staging of cervical cancer was performed through clinical examination using the FIGO (International Federation of Gynaecology and Obstetrics) staging system (Fig 4). MR imaging provides a more accurate method of the stage of cervical cancer than clinical examination. Thus FIGO staging is now based on MR imaging findings rather than clinical examination. Endovaginal ultrasound is used mainly for detection of cervical cancer.

Tumours restricted to the uterus and upper two thirds of the vagina and <4cm in size (Stage IIa or lower) are amenable to surgery. Tumours >4cm in size, involving the distal third of the vagina or extending to the parametrium, pelvic sidewall, rectum or bladder (Stage IIb and higher) are best treated with radiotherapy and chemotherapy. Tumours <2cm in diameter (Stage 1A2 and 1B1) may be treated with fertility sparing surgery if the remaining cervix is >1cm in length.

Early cervical cancer is difficult to detect on ultrasound due to its small size and similar echotexture to normal cervical mucosa. However, published data has shown that up to 93% of invasive cervical cancer is detected by endovaginal ultrasound. Ultrasound features of cervical cancer include abnormal mucosal echotexture, distortion of cervical morphology and loss of compressibility of the cervix. Cervical cancer also shows increased vascularity on Doppler ultrasound in almost all cases (Fig 5). Occasionally the cervix may be totally replaced by tumour and invasion of adjacent organs may be evident on

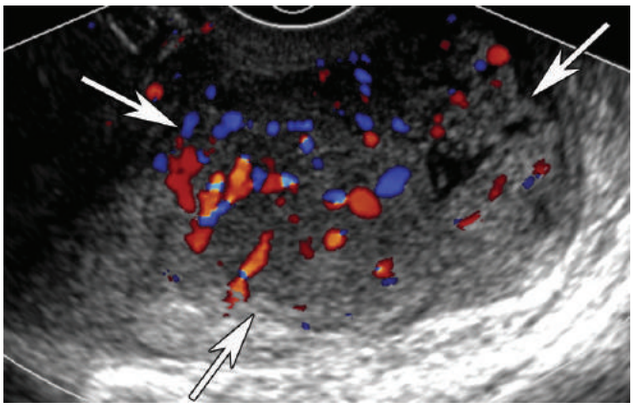


Figure 5. Sagittal endovaginal ultrasound showing a cervical cancer (arrows) that is causing distortion of cervical canal architecture and abnormal echotexture and demonstrates hypervascularity on colour Doppler evaluation.

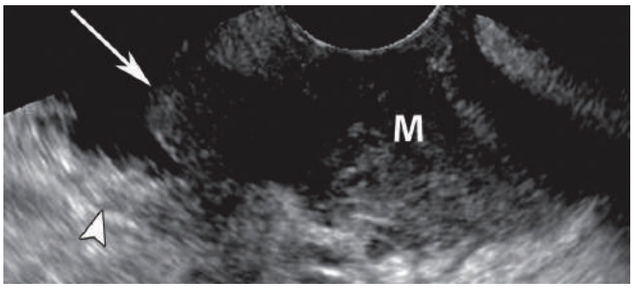


Figure 6. Sagittal endovaginal ultrasound of a locally advanced cervical cancer (M) showing invasion of the bladder wall (arrow). A normal segment of bladder wall (arrowhead) is also seen.

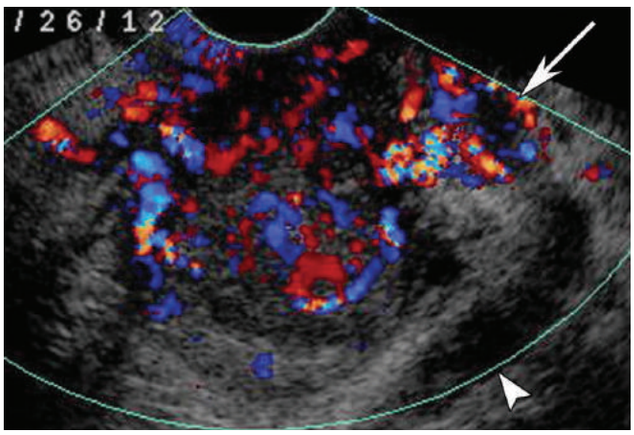


Figure 7. Coronal endovaginal Doppler ultrasound showing a hypervascular tumour with parametrial invasion (arrow) and obstruction of the left ureter (arrowhead).

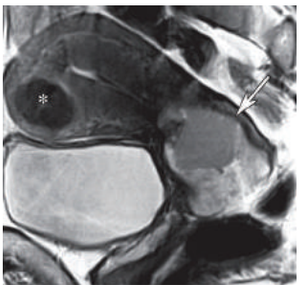


Figure 8. Sagittal T2-weighted image showing a cervical mass (arrow) of mixed hyperintensity that involves all of the cervical canal and extends into the lower uterus, but does not involve the outer stromal layer, vagina or adjacent organs. A fibroid (*) is incidentally noted.

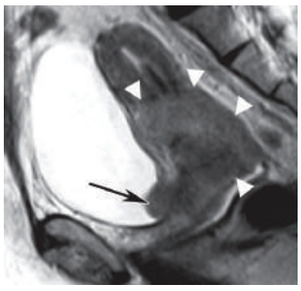


Figure 9. Sagittal T2-weighted image showing an extensive mass (arrowheads) originating from the cervix and involving the uterus and rectum. Extension into the bladder (arrow) is also noted.

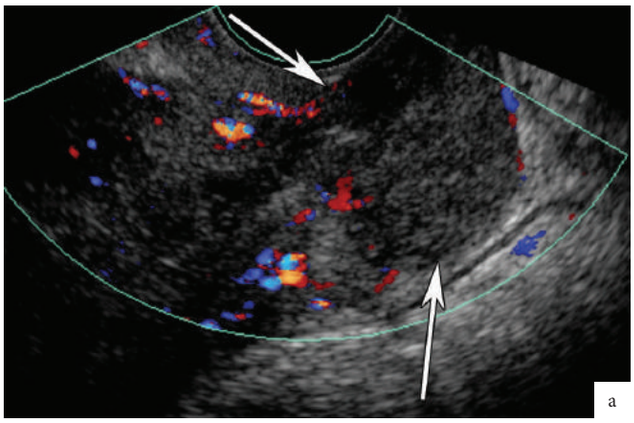
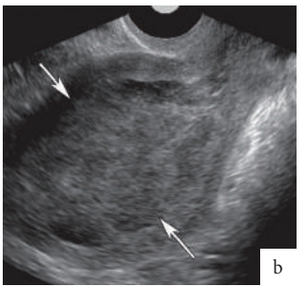


Figure 10a. Sagittal endovaginal ultrasound showing an ill-defined mass in the cervix (arrows).



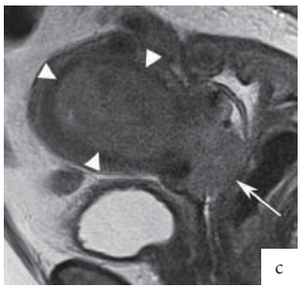


Figure 10b. Sagittal endovaginal ultrasound showing a mass in the endometrial cavity of the uterus (arrows). c. Sagittal T2-weighted MR scan depicting a large mass (arrowheads) extending from the uterine cavity into the cervix and vagina (arrow).

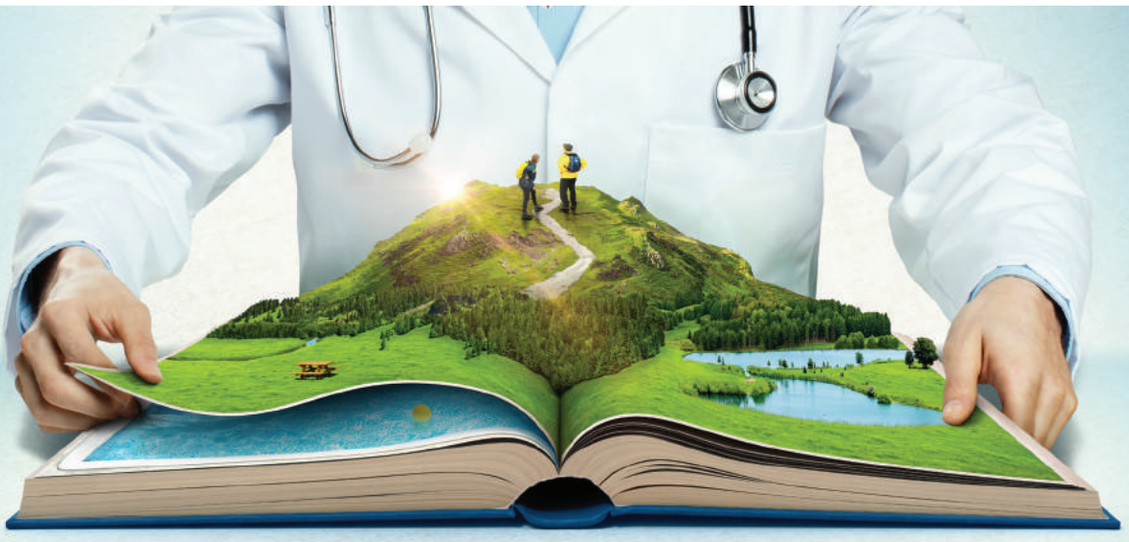
AN INABILITY TO VISUALISE AND DOCUMENT A NORMAL CERVIX MAY OCCASIONALLY BE THE ONLY INDICATOR OF DISEASE IN THE CERVIX

endovaginal ultrasound (Fig 6). Application of pressure on the endovaginal probe evaluates mobility of the cervix in relation to the rectum, bladder and vagina; lack of mobility indicates adjacent organ involvement.

MR imaging provides accurate evaluation of cervical tumour size and invasion of adjacent structures including the bladder, rectum and parametrial regions (Figs 7-9). Evaluation of the retroperitoneum is required particularly in case of larger tumours to detect lymph node metastases and ureteric infiltration with obstruction; this may be performed with computed tomography (CT) or MR imaging.

Occasionally, a mass in the cervix may be due to inferior extension of an endometrial cancer (Fig 10). This condition may be detected on both endovaginal ultrasound and MR imaging, and its distinction is of clinical relevance as the treatment options for the cervical and endometrial cancer differ.

It is important to note that a number of pitfalls exist in relation to ultrasound assessment of cervical cancer. It is common to see a relative lack of images of the cervix in pelvic ultrasound exams. Failure to visualise and document a normal cervix may lead to missed cervical cancer. An inability to visualise and document a normal cervix may occasionally be the only indicator of disease in the cervix. A mass in a grossly distorted cervix may be erroneously interpreted as a uterine fibroid if a normal cervix has not been properly documented. Hydrometra should also be interpreted with caution as obstruction of the cervical canal may be due to a cervical cancer. In cases where ultrasound does not clearly document a normal cervix, where secondary signs are present (e.g. haematometra) or clinical symptoms are persistent and unexplained, it is prudent to proceed to MR imaging.



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[1] 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 mg BID. †Lung function trough 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:** P O M **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 , EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872 2015-MT-ULT-09-OCT-2015

References

1. Wedzicha JA, *et al*. New Engl J Med 2016. N Engl J Med 2016; 374:222-2234. June 9, 2016. DOI: 10.1056/NEJMoa 1516385.
2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

NOVARTIS

ULT Ad1 09/16 MT

thesynapse.net

THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

TRUSTED RESOURCE

CELEBRATING 20 YEARS OF SERVICE

1996 - 2016

Your best resource for:

Medical News · Corporate News · Continuing Medical Education · Local and international Publications

Available on the App Store

ANDROID APP ON Google play