THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

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e-Learning Modules

Protecting Patients' Medical Records under the GDPR

Rare Diseases Why bother?

39th World MediGames, Malta

Asthma Relvar Ellipta is an ICS/LABA for patients (≥12 years) uncontrolled on ICS alone and 'as needed' SABA[1]

Remind her of what she's been missing

Your choice of treatment could mean your patients don't have to miss out.

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 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) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)
Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal
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. Relvar Ellipta Summary of Product Characteristics. GlaxoSmithKline; 2016.

MLT_GIB/FFT/0003/17 Date of preparation: January 2017

Relvar™ Ellipta™ was developed in collaboration with INNOVIVA

GENE EDITING... QUO VADIS?

As discussed in the last editorial, modern gene editing is quite precise but it is not perfect. The procedure can be hit and miss, reaching some cells but not others. Even when Crispr gets where it is needed, the edits can differ from cell to cell, for example mending two copies of a mutated gene in one cell, but only one copy in another. For some genetic diseases this may not matter, but it may if a single mutated gene causes the disorder. Another common problem happens when edits are made at the wrong place in the genome. There can be hundreds of these "off-target" edits that can be dangerous if they disrupt healthy genes or crucial regulatory DNA.

Another controversial milestone is applying this technology in embryos with the added advantage that any edits will be passed on to future offspring [together with any undesirable off-target effects]. This is not science fiction, I repeat. In 2017, *Nature* published research relating to gene editing in embryos made with the sperm of a man who inherited a heart condition known as hypertrophic cardiomyopathy.[1] When the scientists made embryos with the man's sperm and healthy eggs from donors, they found that, as expected, about 50% of embryos carried the mutant gene. If the affected embryos were implanted into women and carried to term, the resulting children would inherit the heart condition. The researchers describe how gene editing, when performed early enough, at the same time as fertilisation, 42 out of 58 embryos, or 72%, were found to be free of the disease-causing mutation. Also in 2017, a similar technology, base editing, has been used to fix defective β-thalassaemia genes in human embryos.[2] Base editing, differs from gene editing in that it does not cut the double helix, but instead uses enzymes to precisely rearrange some of the atoms in one of the four bases that make up DNA or RNA, converting the base into a different one without altering the bases around it.

I know that discussing ethical issues merits more than a few words but let us consider the fact that today, people who carry certain genetic diseases prefer to opt for IVF and have their embryos screened for harmful mutations. If mutations are detected, these embryos are wasted. In specific scenarios, gene editing can help increase the number of embryos for implantation since this technology can eliminate such mutations.

The ramifications arising from such technology are infinite, including gene drives. Engineered gene drives have the power to propagate particular genes through an entire population of organisms, e.g. by implanting a fertility-reducing gene in malaria-carrying mosquitoes with a view to eradicate malaria. But still, this technology is controversial because it can have massive unintended ecological consequences.

REFERENCES

1. Ma H, Marti-Gutierrez N, Park SW, et al. Correction of a pathogenic gene mutation in human embryos. Nature 2017;548(7668):413-419.
2. Liang P, Ding C, Sun H, et al. Correction of β-thalassemia mutant by base editor in human embryos. Protein Cell 2017;8(11):811-822.

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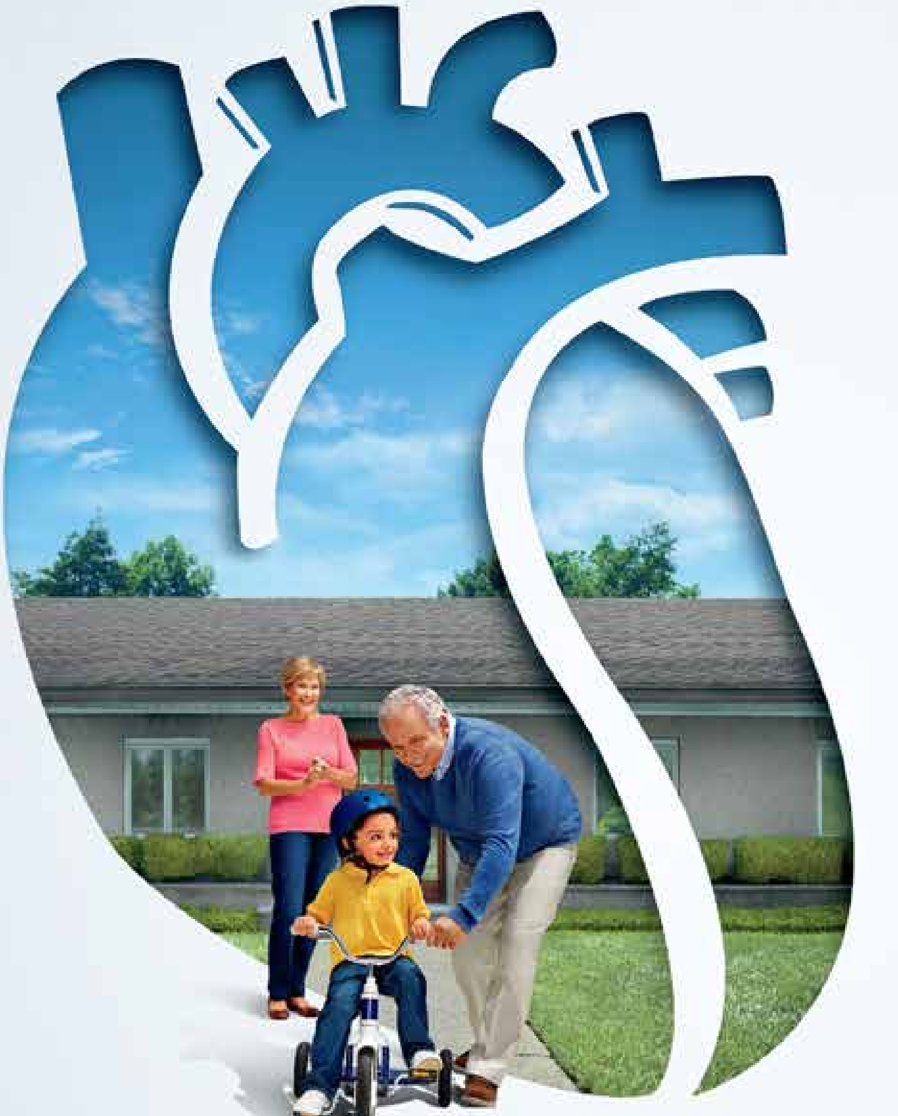
ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE[†] CLASS I RECOMMENDED[3,4]



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

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

† Based on 2016 ESC HF Guidelines and 2017 ACC/AHA/HFSA Guideline Update.

‡ Primary end point.

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

NOVARTIS

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AUTHORS

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Mr Ian Deguara BSc (Business & Computing) (Melit.) occupies the position of Director of Technical Affairs at the Office of the Information and Data Protection Commissioner. His main areas of responsibility include investigating complaints relating to both data protection and freedom of information, advising the Commissioner on various local and European data protection issues, conducting on-site inspections and investigations, actively participating in European working groups on data protection and devising the necessary strategies to implement the new data protection legal framework (GDPR) which shall apply as from 25 May 2018.

ISSUE GUIDE

TheSynapse

PROTECTING PATIENTS' MEDICAL RECORDS UNDER THE GDPR

IAN DEGUARA

The rapid progress in technology and in the field of electronic data processing has radicalised the conventional handling of personal data, leading to increasing risks and vulnerabilities. It is an unchallenged fact that such risks may have a significant effect on the fundamental rights and freedoms of data subjects. The online environment is exposing personal data to security breaches, hacking and other unlawful forms of processing, regretfully to the detriment of the individuals' privacy rights. The recent Facebook scandal involving the sharing of users' personal data with Cambridge Analytica speaks for itself!

The need for a major reform in the European data protection framework, led the European Commission, in January 2012, to publish a proposal for the General Data Protection Regulation (GDPR). The GDPR is one of the most wide-ranging pieces of legislation adopted by the EU in recent years. It aims to establish accountability, consistency and harmonization across the EU, rebalance rights in the digital world and provide legal certainty for economic operators. Harmonization was a key element in the decision taken by the Commission in the choice of the legal instrument. In fact, a regulation was chosen as the most appropriate instrument to be adopted for the GDPR due to its binding effect and direct applicability in all Member States.

After a long negotiation process at European level, the GDPR came into force on 25 May 2016. It provided for a transitional period of two years for data controllers to familiarise themselves with the new provisions and align the processing operations involving personal data with the new rules. The GDPR will therefore start to apply on 25 May 2018 and will replace the twenty-year-old Directive 95/46/EC.

The GDPR will not bring about a revolution in the way personal data are processed, but it is an evolution of the current legal framework. If one had to compare the principles and legal criteria of the current Directive against those set out under the GDPR, the conclusion is that the same principles and criteria have indeed withstood the test of time and have not changed. Having said this, the GDPR provides for stronger rules on data protection, which effectively mean that data subjects will have more control over their personal data and business operators will benefit from a level playing field.

A medical professional, operating as a self-employed, is the data controller responsible for determining the means and purposes of the patients' health records collected during the exercise of the professional duties.

As previously considered by the current Directive, medical records constitute special categories of personal data, as the processing can create significant risks to the data subject's fundamental rights and freedoms. The GDPR now expressly includes "genetic data" and "biometric data" within this category, particularly when the latter is processed 'through a specific technical means allowing the unique identification or authentication of a natural person'.

Although the rule dictates that the processing of special categories of personal data is prohibited, article 9(2) of the GDPR provides, in a closely replicated fashion to the present Directive, the grounds to process such data in the area of health and healthcare management. Therefore, the processing is legitimised if one of the following criteria applies:

- the data subject has given his explicit consent, unless reliance on consent is prohibited by EU or Member State law;
- processing is necessary for the carrying out of obligations under employment, social security or social protection law, or a collective agreement;
- processing is necessary to protect the vital interests of a data subject who is physically or legally incapable of giving consent;
- processing is necessary for the purposes of preventative or occupational medicine, for assessing the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment or management of health or social care systems and services on the basis of Union or Member State law or a contract with a health professional;
- processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health or ensuring high standards of healthcare and/of medicinal products or medical devices.

Article 9(2)(j) sets a new provision for the processing of personal data for the purposes of archiving and research and statistics, subject to appropriate safeguards. Those safeguards shall ensure that technical and organisational measures are in place to guarantee respect for the principle of data minimisation. These measures may include pseudonymisation, which provides that the

IF THE [DATA] PROCESSING CONCERNS PERSONAL DATA FROM PATIENTS OR CLIENTS BY AN INDIVIDUAL PHYSICIAN ... A DATA PROTECTION IMPACT ASSESSMENT SHOULD NOT BE MANDATORY

personal data can no longer be attributed to a specific data subject without the use of additional information and that the additional information is held separately. Additionally, further processing of personal data for scientific research purposes shall not be incompatible with the original processing purposes.

The principles of storage and purpose limitation apply to medical records too. Retention should not be longer than necessary. In the process of determining a justifiable timeframe, the applicable legal and operational requirements should be taken into consideration. Furthermore, when personal data are processed solely for scientific research it may be stored for longer periods. However, in both cases, appropriate technical and organisational safeguards have to be adopted.

Under the current law, health professionals already have the obligation to provide certain information to patients about the processing of personal data, including but not limited to, the purposes of processing, categories of recipients with whom the data may be shared and also, data subjects' rights. However, the GDPR expands the list and sets out that data controllers shall provide information on how long they will store the data, the existence of any automated-decision making and the right to lodge a complaint with the supervisory authority. Although there may be other acceptable approaches to fulfil this obligation, the preferred practice should be for health professionals to develop a privacy policy and make it accessible to their patients.

As from 25 May 2018, data controllers will be obliged to carry out a data protection impact assessment (DPIA) where processing is likely to result in a high risk to the rights and freedoms of individuals. A DPIA involves an assessment of the probability and severity of the risks involved in the proposed data processing as well as the measures and safeguards to be introduced to mitigate such risks. Having said this, it is relevant to make reference to recital 91 of the GDPR which specifically provides that "*the processing of personal data should not be considered to be on a large scale if the processing concerns personal data from patients or clients by an individual physician, other health care professional or lawyer. In such cases, a data protection impact assessment should not be mandatory*".

The GDPR also introduces an obligation on data controllers to report breaches of patients' health records to the data protection authority within 72 hours from becoming aware of the incident. A personal data breach is defined as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. If the breach is likely to result in a high risk to patients, for instance, the compromised

THE MAXIMUM ADMINISTRATIVE FINE CONTEMPLATED BY THE GDPR IS OF 20 MILLION EURO OR 4% OF A COMPANY'S GLOBAL ANNUAL TURNOVER IN CASE OF AN INFRINGEMENT

electronic health records were not encrypted and no measures could be taken to reduce the risk, the health professional would be required to notify all the affected individuals.

With the GDPR, data subjects have new rights, such as the right to data portability. This means that where the data subject has provided the personal data and the processing is based on consent or on a contract, the data subject shall have the right to request the transmission of those personal data which are retained by an automated processing system (no paper records).

Existing rights have been strengthened, in particular, the right to erasure and the right of access. Exercising a right of access entitles patients to request copies of their medical records. When acceding to such right, the health care professional must ensure that any information identifying third parties is redacted or blanked out; most importantly, health care professionals must always be guided by their primary responsibility to act in the best interests of their patients.

Whether health data are collected, stored or accessed via wearable devices, mobile applications, cloud computing capabilities or databases, security of health records must be placed at the top of the priority list, since any misuse may have irreversible consequences for the data subject. Both the controller and the processor share the responsibility to implement appropriate technical and organisational measures to ensure a level of security appropriate to the risk. Such measures may include encryption, pseudonymisation, and the ability to restore the availability and access to personal data in a timely manner in the event of a physical or technical incident. Physical security must not be overlooked since it plays an equally important role in the security chain.

It is pertinent to note that the maximum administrative fine contemplated by the GDPR is of 20 million Euro or 4% of a company's global annual turnover in case of an infringement. This might very well be a reason why the GDPR has become the talk of the town over the past months.

A final take-away message is that, if you are not able to protect, do not collect!

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

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

FLAME STUDY RESULTS[1]

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

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

*Fluticasone/salmeterol 500/50 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:* As with other inhalation therapy, administration of Ultibro Breezhaler may result in paradoxical bronchospasm which 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, dyspepsia, dental caries, bladder obstruction and urinary retention., cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia musculoskeletal pain, pruritis/rash musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, gastroenteritis tachycardia, palpitations, , insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872

2016-MT-ULT-10-NOV-2016

References

1. Wedzicha JA, *et al.* Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34
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RARE DISEASES

WHY BOTHER?

DR FRANCIS AGIUS

DEFINITION

Rare diseases are those diseases that affect a small number of people when compared to the general population. In 2009 the EU adopted the definition that a rare disease has a prevalence of less than five persons being affected out of 10 000 persons.[1] An important estimation is that 8% of the population is born with, or develops, a rare disorder over their lifetime. Thus, it is estimated that around 30 million Europeans suffer from a rare disease. Based on the same assumption, the Maltese rare disease population should be around 25,000 patients. The EU definition further states that rare diseases are life-threatening or chronically debilitating conditions. About 80% of rare diseases have a genetic origin, being either monogenic or polygenic.

RELEVANCE TO GENERAL PRACTICE AND GENERAL PRACTITIONERS

Published information about the primary care role in rare diseases is very scant. The response to rare disease by organisations such as the US National Organization of Rare Disorders [NORD] and the European Organisation for Rare Diseases [EURORDIS] has focused on making information more accessible and on coordinating research efforts into rare conditions. This approach seeks to connect isolated patients with specialised knowledge and specialist clinicians. However, general practitioners also see rare conditions frequently.[2,3] EURORDIS is the pan-European organization established through a coalition of patient-support groups and the European Union back in 1997. Eurordis lists the problems faced by patients with rare diseases and their families as lack of access to the correct diagnosis, lack of scientific knowledge, lack of appropriate quality healthcare, high cost of the few existing drugs and care and inequities in treatment and care between different countries.[4]

It is highly likely that general practitioners (GPs) will regularly manage patients with rare disorders. Paradoxically, rare diseases are common; in fact GPs care for those 8% of the population classified as having a rare disease. This is similar to the proportion of people living with diabetes or asthma. Based on an estimate of 349 GPs in Malta,[5] and assuming same practice numbers (of around 1200 individuals), each GP on average would theoretically have 99 rare disease patients under their care. In keeping with this, in a French study 26% of children who attended a disability clinic had disabilities related to a rare disease.[6] This exemplifies the significant humanistic and economic impact on families, society and health services posed by such rare diseases. Clinicians therefore need easy access to educational opportunities and information resources about rare diseases.

THE DIAGNOSTIC ODYSSEY

A delayed diagnosis, usually 5-30 years, is reported in 25-40% of cases and 40% are initially given an incorrect diagnosis.[7] A delayed diagnosis of a treatable condition can lead to severe irreversible and life-threatening consequences. Moreover, parents of a child with an undiagnosed, rare and inherited condition may go on to have a second child with the same condition. The value of diagnosis cannot be underestimated, even in the absence of an effective treatment. Without a diagnosis, individuals lack a narrative to explain their symptoms and end up having to defend

their right to access healthcare and support.[8] The lack of diagnosis leads to frustration and helplessness and may adversely affect the doctor-patient relationship.[9]

MALTA AND RARE DISEASES

The overarching aim of any national rare diseases initiative is to reduce the burden caused by rare diseases through combined efforts at multiple levels to identify and implement primary preventive measures, and, where possible to reduce the number of people affected by a rare disease. Furthermore, one should ensure earlier diagnosis and appropriate management, prevent premature death, preserve and enhance patients' quality of life and socio-economic potential and improve access to care (both in healthcare and in other sectors of services such as education and social services).[10]

Malta has a number of initiatives in place to favour the rare disease patient. Patients requiring treatment for specific rare diseases are referred abroad, mainly through a bilateral health agreement between Malta and the UK. The Maltese Ministry for Health electronic portal also has a dedicated section for rare disease with links to relevant rare disease sites (www.rarediseases.gov.mt). An important feature is the rare disease report form which can be filled online whenever a GP encounters a known or suspected case of rare disease.[11]

With regards to orphan drugs, the Maltese government reimburses the cost to patients within the national health scheme. As of 2013, there were 39 licensed orphan medicinal products in Malta. Also, during 2013 Malta actively began looking at the feasibility of introducing a suitable coding system for orphan medicinal products [Orphacodes].[12]

Malta currently faces considerable barriers to the prevention, diagnosis and treatment of rare diseases primarily due to insufficient knowledge of the individual and collective epidemiology of these conditions. Misdiagnosis, delays in diagnosis and inadequate treatment may occur in view of clinicians' infrequent encounters with rare disease patients. Their limited experience often makes early diagnosis and implementation of treatment and support a challenge. Little or no specific training concerning rare diseases is given to medical and other healthcare students, with exposure to cases during the medical training and subsequent career being limited to opportunistic or chance encounters and examinations. There is still complex and incomplete access to adequate care most of the time. This may stem from the fact that research on rare diseases is still underdeveloped locally.[13]

WHAT IS THE ROLE OF THE GP IN PATIENTS WITH RARE DISEASE?

Many patients with rare diseases will present their symptoms first to a GP. They will also attend a GP in between visits to the specialist, requiring diagnosis and treatment of common ailments, and will benefit from the preventive health services offered. They will require the accessible, relationship-based advocacy and support role that is at the heart of good general practice. The same GP will often perform this role for the patients' carers. A thoughtful, proactive, ongoing response in the context of a continuing relationship with a GP may reduce many of the negative experiences of patients with rare diseases.[14] Anderson et al showed that 80% of children with a rare disease had visited their GP at least once in the 12 months preceding the conduct of the study, with an average of eight visits and a range of 1-240 visits each.[15] Thus it is important that a detailed family history, careful documentation of presenting symptoms and signs, as well as prompt referral to specialist services is made to decrease any diagnostic delays (the infamous diagnostic odyssey) and allow for earlier and hence more effective intervention.[14] This is more relevant for the Maltese health system, wherein patients may tend to seek more and more specialist opinions as the diagnosis starts becoming more elusive. Each specialist is likely to concentrate of his/her area and may give conflicting advice to that received from another specialist of another specialty. The GP is the only health professional who would have a holistic view of the patient's diagnostic journey and is in the best position to be the navigator guiding the patient even though any specialist consultation, thus helping to maintain safety and shorten the time till diagnosis.

INFORMATION AND TRAINING

No GP is expected to have detailed knowledge of even a fraction of the huge number of known rare diseases. It is not even possible to adequately cover rare diseases in undergraduate or postgraduate medical training. In France, raising awareness and identifying sources of information is provided through a 2 hour training session to all health professionals.[16] Maltese GPs can access educational resources through several information portals including Orphanet (www.orpha.net), Centre for Genetics Education (www.genetics.edu.au), Online Mendelian Inheritance in Man (OMIM; www.omim.org) and the National Institutes of Health, Genetic and Rare Diseases Information Centre (rarediseases.info.nih.gov).

WHAT IS ORPHANET?

Orphanet was established in 1997 and is a European website providing encyclopaedic information and classification of rare diseases (search by disease or by symptom). It has a directory of patient organisations as well as a directory of ongoing clinical trials and research studies. It also provides an inventory of orphan drugs, centres of excellence, specialized medical laboratories and patient-support groups.[17] Orphanet was followed by a national plan for rare diseases in Europe in 2004, which was the first of its kind in the world.

PATIENTS REQUIRING TREATMENT FOR SPECIFIC RARE DISEASES ARE REFERRED ABROAD, MAINLY THROUGH A BILATERAL HEALTH AGREEMENT BETWEEN MALTA AND THE UK

CONCLUSION

A comprehensive approach to the management of rare disease in primary care is needed in Malta, developed in consultation with the medical profession. In keeping with this, when GPs are visited by rare disease patients, the following six points should always be kept in mind:[14]

Diagnose. Ask more frequently "Could it be a rare disease?" Recognise deviations from common patterns of disease. Be judicious in testing for low-prevalence disorders. Help the patient navigate and use wisely specialist services for precise diagnoses.

Attend to the whole patient. Provide high-quality care for other health issues including unrelated common conditions and preventive activities (e.g. immunisation, screening and health promotion).

Know the disease. Become knowledgeable about the rare diseases encountered, including natural history, evidence-based treatment options, systematic long-term care, associated problems, and genetics. Seek out appropriate specialist services, international centres of excellence, and local organisations which offer relevant services.

Empower the patient. Encourage patients and their carers to ask questions, and assist them with self-care and decision making.

Support the family. Contribute to the physical, emotional, psychological, spiritual and social needs of the patient's support network.

Advocate. Support the patient's journey through social service and medical bureaucracies, and interpret any written and verbal information.

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SHORT ACCOUNTS OF INTERESTING CASES, SOME MEDICAL DISASTERS, INVOLVING PATHOLOGY AND CLINICAL PRACTICE, FROM THE RECOLLECTION OF PROF. ALBERT CILIA-VINCENTI.

OVARIAN CANCER OR NOT?

This is now the second half of the 1980s, I've been a consultant surgical pathologist at the Royal Hampshire County Hospital in Winchester since 1980, and I get a phone call from a friend in Malta who says his wife has just been diagnosed with ovarian cancer and asking me whether I would mind reviewing the histological slides before she starts chemotherapy. No problem – confirming ovarian cancer should be straightforward.

This lady was around 50 years old and had consulted her doctor, and then a gynaecologist, because of some pain and redness around her umbilicus. A right ovarian mass was diagnosed and she underwent a bilateral oophorectomy and total hysterectomy. At operation, besides the right ovarian mass and some fluid in the pelvic cavity, a portion of omentum was found stuck in a small umbilical hernia, was extracted from the hernia sac, excised and also sent for pathological examination.

The perimenopausal uterus and left ovary were unremarkable on the histological sections. The right ovarian mass looked like a serous cystadenoma, but serous cystadenoma type cells were noted sitting on the peritoneal surface of the ovarian cystic tumour. Furthermore, there were small well-circumscribed nests of similar serous well-differentiated neoplastic cells in the portion of omentum removed from the umbilical hernia sac. These findings had been interpreted in Malta as a well-differentiated ovarian serous cystadenocarcinoma with omental and peritoneal cavity spread.

Fortune would have it that I had just come across a paper by Steven Russell, an Australian pathologist claiming, that a previously unrecognised category of ovarian neoplasia, was a serous cystadenoma-like ovarian mass often accompanied by what he called "benign implants" (looking like mini serous cystadenomas) in the omentum and on pelvic peritoneal surfaces. He claimed this was not malignant metastatic disease but a "field change" within the female pelvic peritoneal cavity resulting in multiple locally-arising (non-metastatic) tiny serous cystadenoma-like "benign implants". He also claimed that very often these "benign implants" regressed after the main ovarian tumour was removed.

How had he reached this rather implausible story? He claimed he had reviewed his department's ovarian cancer records and found that a small number of patients were still alive a number of decades later, suggesting incorrect diagnoses. On reviewing their histological findings he came to the conclusion that these cases represented a category of multifocal Mullerian serous neoplasia that was not fatal and that could be adequately controlled and cured surgically without any need for chemotherapy. Some years later, when his findings were confirmed in the US and Europe, this category of ovarian neoplasia became known as "serous ovarian tumour of borderline malignancy".

I phoned her husband to tell him that I did not think she had ovarian cancer and sent him a brief written statement of my opinion based on the fact that his wife's findings tallied with Russell's descriptions of this "new" category of non-fatal ovarian neoplasia. I then got a call from Professor Frederick Fenech, a personal friend of the husband, who asked me whether I was sure she needed no further action but only observation. I replied that if she was my wife, that is all I would recommend.

The husband asked me to arrange a consultation for his wife with a London gynaecologist. Her histological slides were also reviewed by a London pathologist and reported as serous cystadenocarcinoma with peritoneal and omental metastatic spread – same as the Malta diagnosis. The couple came to London where a scan was reported to have found a recurrent mass in the right iliac fossa and the gynaecologist recommended an exploratory laparotomy. Distressed and confused, the couple declined further surgery in London and returned to Malta where, a repeat scan by Dr Malcolm Crockford, found gas in the caecum and no mass in the right iliac fossa.

This lady had no further treatment, is now in her eighties and enjoys excellent health. Her husband suffered from ischaemic heart disease and died suddenly several years ago.

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THE 39th World Medical & Health Games ARE COMING TO MALTA

Sports Director **Pierre Chicco** talks Medigames with TheSynapse.

TS: WHAT ARE THE WORLD MEDICAL & HEALTH GAMES, OR MEDIGAMES FOR SHORT?

The World Medical & Health Games are the world's largest sporting event for health professionals, created in 1978 by the French Newspaper, *Le Quotidien du Médecin*, with the purpose of bringing together professionals in the field of sports medicine. Since its start the event changed hands, but has maintained the great momentum and passion with which it was started, to become what it is today. Following a string of yearly Medigames at such places as Canada, France, Ireland, Austria, Hungary and many others, this year the 39th edition of the World Medical and Health is being held in Malta **for the first time**.

TS: WHAT HAPPENS DURING THIS WORLD-FAMOUS SPORTING HEALTH EVENT?

The event itself is a week-long getaway for professionals and students in the health sector and it is as much a vacation as it is a professional event. Every year, up to **2000 participants from over 40 nationalities** come together to compete in the Olympic spirit. You can say the event is three-fold: there are sports games for 26 disciplines - athletics, tennis, sailing, football, basketball … and everything in between; an international sports medicine symposium; as well as a networking event. Each part is important, but we pride ourselves in creating a platform where professionals and students in the sports medicine sector can meet their peers from the international sphere. Every year this proves to be an excellent opportunity to share ideas, socialise, relax and have fun, meet old friends and make new ones, and clinching connections for life, while indulging in the sports, participants are so passionate about.

TS: WHAT IS YOUR ROLE IN THESE GAMES?

I love sports and have always wanted to work in sports and sporting events. I've been organising the World Medical & Health Games since 2006 - it has given me great pleasure to successfully organise this event across the world; it is also most satisfying to see this event grow, year after year.

TS: WHY DID YOU CHOOSE MALTA AS A DESTINATION FOR THIS YEAR'S MEDIGAMES?

We had already organised another sporting event in Malta back in 2015, and it was quite a success. I think Malta is a great destination for the World Medical & Health Games for many reasons. For starters it is perfect as a touristic location, and offers our participants a fantastic holiday destination with good weather, lots of history, nature and sea. Moreover, it has many well-equipped sporting venues, which due to the country's size are all within easy reach. Not to mention the good flight connection. It is imperative that this event is not just a sports

The French team of beach volleyball during the semi-final, Catalans Beach, Marseille (France)

competition event, but a relaxing, exciting and informative experience for those who participate, and Malta is perfect to make that happen.

Moreover, we have had a great response both from the authorities and professionals alike. Malta Tourism Authority is our main sponsor and Sports Malta has helped us a lot too, as well as Air Malta, Conventions Malta and our destination management company, MPE.

There are also Maltese professionals involved in the event, notably Dr Lucienne Attard, a sport physician - also secretary of the Maltese Association for Sports & Exercise Medicine, executive board member for the Maltese Olympic Committee and Chairperson of the National Anti-Doping Organisation - who was very supportive and helpful. Dr Danica Bonello Spiteri, a sports physician and athlete, and Robert Grech, President of Osteopathy Malta, were very involved and supportive of the event too.

TS: WHAT ARE THE MAIN POINTS OF THE SYMPOSIUM?

The symposium is the cornerstone of this event; it is where professionals come together to keep themselves updated about important topics. Accredited by the UEMS (European Union of Medical Specialists), the symposium is chaired by Dr André Monroche (President of the French Society of Exercise and Sport Medicine between 2001 and 2005) and vice-chaired by Prof. Xavier Bigard (medical director of the International Cycling Union, scientific advisor to the French Anti-Doping Agency, and President of the French Society of Exercise and Sport Medicine till December 2017).

This year's main theme is *Lower Limb Pathologies in Sport*, and the three sub-themes are *Exercise of Sports Medicine in France and the World*, *Sports in Hot Countries*, and *Doping Prevention*. The symposium programme is divided in two, one session dedicated to the symposium sub-themes and another session dedicated to free scientific communication, when the floor is opened to anyone wishing to discuss a paper or topic they wish.

This presents an opportunity for local professionals in sports medicine, as well as students interested in pursuing a career in this sector, to share their expertise in this year's themes as well as benefit from the information and connections that come with an event like this.

Prof. Xavier Bigard, Vice-President of the International Sport Medicine Symposium - Marseille (France)

Start of the second stage of cycling - Marseille (France)

TS: IMPORTANT DETAILS TO REMEMBER?

The 39th World Medical & Health Games will held from the 16 till the 23 June within the Olympic Village which is going to be based in St Paul's Bay. Registration for the event can be done online at www.medigames.com with a point of contact at info@medigames.com. It is open for all health professionals and health students; there are also sports and educational activities for children under 16 years of age, to ensure that the event is as family friendly as possible. We hope that a maximum of Maltese participants will come to share this week of sports, confraternity and scientific exchange.

2nd sailing regatta in the harbour of Marseille (France)

Javelin competition - Matin Wohlwend, Norway Team - Bronze medal

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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 metformin, in combination with thiazolidinediones, 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 dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. 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. 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. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustment are necessary in elderly patients (≥ 65 years). **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 and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued. If acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with 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. **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:** Monotherapy: Common (>=1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM. **PACK SIZES:** 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/005. **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 21222572. 2017-MT-GAL-09-MAR-2017

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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. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 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. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's 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 at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. 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. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.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 due to an increased risk of lactic acidosis, iodinated contrast agents, 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 and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop 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, dizziness, fatigue. 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/1/07/425/021, EU/1/07/425/027. 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 21222572. 2016-MT-EUD-12-DEC-2016

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Galvus vildagliptin Eucreas

DR PIERRE VASSALLO

PART II

IMAGING BREAST IMPLANT RUPTURE

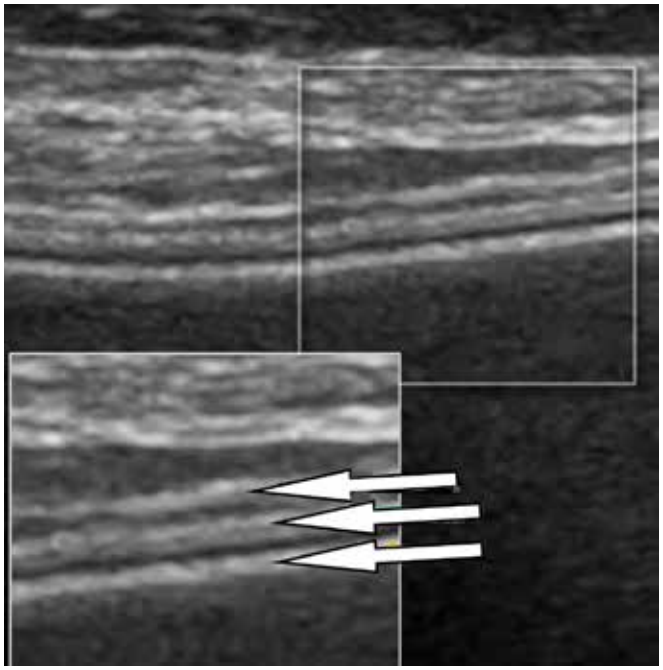

Figure 4: The trilaminar structure (arrows) of the shell-capsule complex seen on ultrasound.

ULTRASOUND

Breast ultrasound is superior to mammography for detection of breast implant leaks but less accurate than breast MRI. Given the wide availability and low cost of breast ultrasound compared to breast MRI, it has become a very important tool. Since its negative predictive value for detecting leaks is high,[4] breast ultrasound is often used as a first examination before proceeding to MRI for more accurate assessment of prosthesis integrity.

A single lumen silicone implant appears anechoic with no internal features on ultrasound. Implants fold themselves within the surgical pocket created by the plastic surgeon; these folds should not be mistaken for implant leaks. With time, a fibrous capsule forms around the implant; this capsule and the implant shell form a capsule-shell complex that appears as three parallel echogenic lines on ultrasound (Fig 4).

Intracapsular leaks may appear on ultrasound as echogenic material deep to the capsule or as an interruption of the capsule-shell complex (Fig 5a). They may also present as echogenic material between the layers of the capsule-shell complex (Fig 5b). An intracapsular tear may also result in complex folding

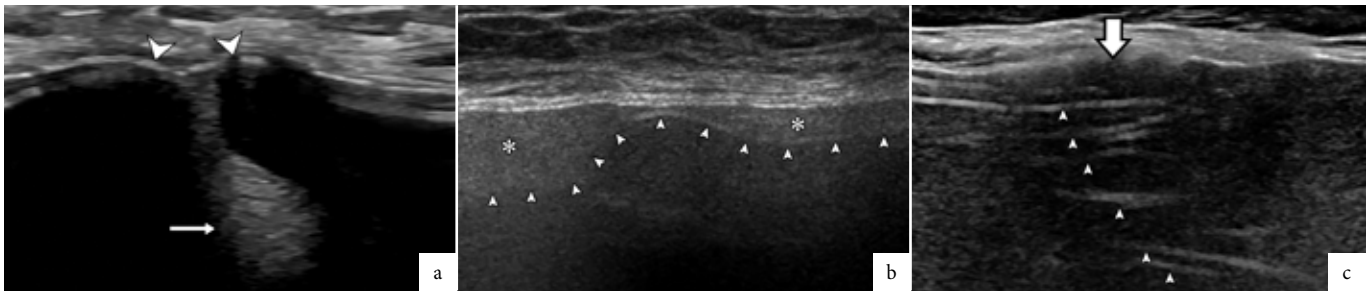

Figure 5: a. Ultrasound shows echogenic material (arrow) deep to the capsule-shell complex and loss of the trilaminar structure of the capsule-shell complex (arrowheads).
b. Ultrasound showing echogenic material (*) between the layers of the capsule-shell complex (displaced shell shown with arrowheads).
c. Ultrasound showing complex folding of the implant shell (arrowheads) known as the step-ladder sign and disruption of the trilaminar capsule-shell complex (arrow).

of the implant shell known as the step-ladder sign (Fig 5c). It is important not to confuse normal implant folds with an intracapsular leak.

An extracapsular leak presents as echogenic material (silicone) within the soft tissues of the breast with no delimiting trilaminar complex (Fig 6a). Free silicone may also be present in the axillary lymph nodes (Fig 6b).

BREAST MRI

MRI is the most accurate imaging modality to assess breast implant integrity. In the US, the food and drug administration recommends a breast MRI three years after implant surgery and bi-yearly thereafter to monitor implant integrity. However, this is not universally accepted since there is no clear evidence that it will influence patient morbidity.

Careful questioning of patients prior to breast MRI is required; saline-filled implants do not require MRI evaluation, while *the presence of tissue expanders (implants that can be filled by external injection of saline) are a contraindication to MRI, because they contain magnets at the injection port.* Only silicone-filled implants should undergo MRI examination.

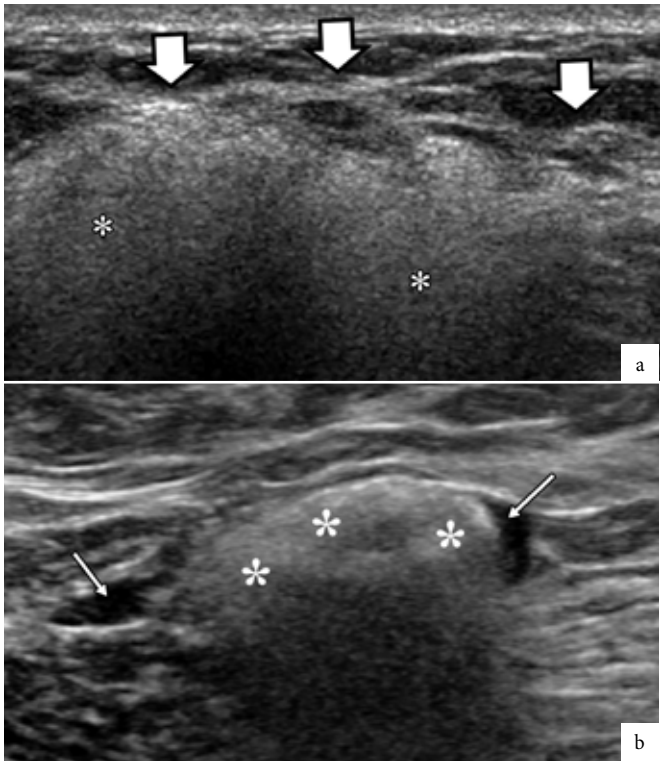

Figure 6: a. Ultrasound showing echogenic material (*) within the soft tissues of the breast with no limiting capsule-shell complex (arrows), which confirms an extracapsular leak. **b.** Ultrasound showing an axillary lymph node (between arrows) containing echogenic free silicone (*).

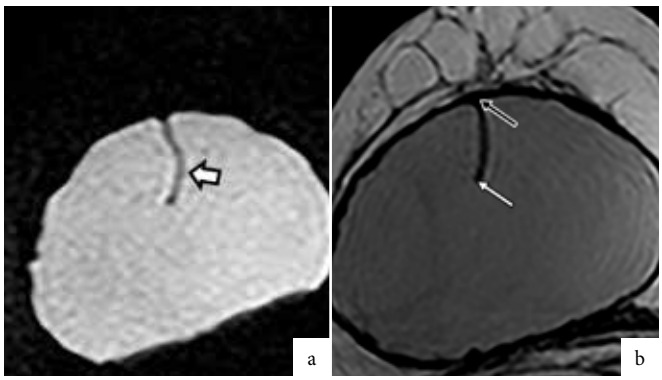

Figure 7: a. A silicone only MR image showing a normal fold in the implant shell (arrow). **b.** A T2-weighted MR image showing low fat signal and intermediate silicone signal depicting a detailed breast tissue anatomy.

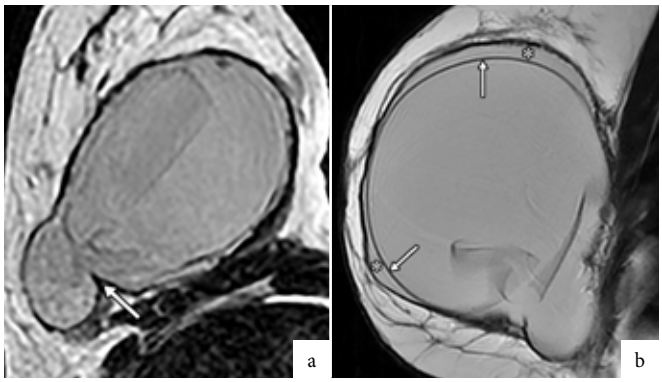

Figure 8: a. Implant herniation (arrow) seen on this T2-weighted MR image. **b.** T2-weighted MR showing free silicone (*) between the capsule and the implant shell (arrows).

The augmented breast contains fat, water and silicone, and MRI can analyse each of these components separately clearly mapping each one within the breast. MRI sequences that null out fat and water clearly depict extracapsular silicone (Fig 7a), while sequences that null out silicone can distinguish a silicone leak from a fluid collection (Fig 7b).

MRI allows accurate assessment of the posterior margin of the implant, which is difficult to see on ultrasound. Implant herniations through the capsule are best seen on MRI and although they do not constitute a leak, they will result in contour deformity (Fig 8a). The presence of free silicone between the implant shell and the capsule can readily confirm an intracapsular rupture (Fig 8b). On the other hand, the classical "linguine" sign, which correlates with the complex folds of the collapsed implant shell, may also occur with intracapsular rupture (Fig 8c).

Extracapsular tears and the presence of free silicone in the axillary tissues and lymph nodes can be readily evaluated with silicone selective MR imaging (Fig 9). Implant assessment MR

EXTRACAPSULAR SILICONE LEAKS MAY SOMETIMES MIMIC BREAST CANCER ON MAMMOGRAPHY AND ULTRASOUND; BREAST MRI CAN DISTINGUISH THE TWO ENTITIES AND THEREFORE IS A VALUABLE TOOL WHEN ASSESSING PATIENTS WITH A HIGH-RISK FOR BREAST CANCER WHO HAVE HAD BREAST AUGMENTATION

protocols must be clearly distinguished from breast cancer screening protocols. The latter require injection of intravenous contrast agent. However, both protocols can be combined if required, delivering the best analysis of implant integrity and the most accurate screening method for breast cancer.

Extracapsular silicone leaks may sometimes mimic breast cancer on mammography and ultrasound; breast MRI can distinguish the two entities and therefore is a valuable tool when assessing patients with a high-risk for breast cancer who have had breast augmentation.

The new generation of breast implants are composed of semi-solid silicone gel (cohesive or "gummy bear" implants). These designs are aimed at reducing the risk of free silicone migration into soft tissue. These implants have been noted to fracture rather than leak; these fractures are best evaluated with breast MRI.

CONCLUSION

Breast imaging is one of the most commonly performed diagnostic imaging studies. Although breast imaging is mainly aimed at detecting early breast cancer, an increasing number of women who attend breast cancer screening have had breast augmentation procedures. It is important to recognise the radiological findings related to breast implant leaks as they may mimic breast cancer. Breast implant imaging is also important when planning management of implant leaks.

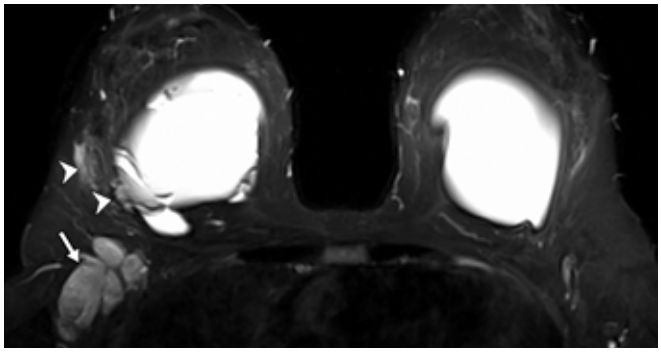

Figure 9: MR silicone image showing an extracapsular rupture (arrowheads) in the lateral aspect of the right breast and silicone within the right axillary lymph nodes (arrow).

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EDITOR'S PICK FOR BOOKWORMS

MADDY'S PANDORA:
CHERRY BLOSSOMS AND CLINICAL CHEMISTRY

''Every single one of us has a story to tell." This story revolves around two girls of the same age with initially apparently very little in common characterwise, called Madeleine and Madison Moretti. One is an intelligent and hardworking medical doctor interested in clinical chemistry, the other seemingly a Japanese pop culture expert, and a manga, anime and gaming enthusiast with deep roots in the land of the rising sun where the cherry blossoms fall.

The story is rich with interspersed cultural and comedic elements. Flipping seamlessly from Madeleine's medical drama to Madison's everyday life and her figurine and keychain collections, unexpected revelations are made. Moving from daily routines to illusions beyond the looking glass that transcend the mortal realm, to the vermillion gates of Inari, and the Coomassie's brilliant blue waters, even deeper secrets surface at the end. The girls touch upon the artefact called romantic love with its many shapes and guises, ranging from Tietz's fiancee, the unique allure of virtual characters, and a fateful chance meeting. Philosophical musing on what constitutes true `happiness' after a potentially fatal incident, and the strong thematic element of duality, blend in to make the story more intuitive and accessible.

It incorporates suspense, and final realisations as to who Madison and Madeleine really were, or who they could have been, with depiction of chemical pathology through the eyes of a girl and references drawn from famous Japanese pop culture elements by a girl who's story could no longer be told.

Source: www.amazon.com

Author: Dr Michelle Muscat
Publisher: i2i Publishing
Published: December 2017
Pages: 200
Price: £8.95

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