THESYNAPSE

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THE MEDICAL PROFESSIONALS' NETWORK

Volume 13 Issue 03

THESYNAPSE

Complete Vaccine Resource

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The Medical Professionals Network, with the help of an educational grant from Pfizer, have collaborated to develop a new vaccine module in TheSynapse mobile application. The new vaccine module guides health care professionals on the various vaccines available, and which vaccine one is recommended to get according to his or her age to prevent diseases of various forms. This can help to ensure that nobody misses out on any vaccines and therefore avoid specific diseases. Having this information in a mobile application can ensure that the doctor gives accurate and timely answers to the questions that may arise with regards to the vaccine, and frequency of administration. This useful and easily accessible guide for medical professionals lists all vaccines available from the National Immunisation Service and those available privately.

TheSynapse Mobile App is being endorsed by the ACIP (Advisory Committee on Immunisation Policy Malta) and the Malta College of Family Doctors.

LAUNCH OF THE NEW VACCINE MODULE

Dr Victoria Sant' Angelo, Manager
National Immunisation Service

Dr Charmaine Gauci, Chairperson
Advisory Community on Immunisation
Policy Malta (ACIP)

"The development of mobile applications for the medical world is a now a global reality and TheSynapse is pleased to be able to provide a tool with local relevance that will help health care professionals in their daily practice."
Dr Wilfred Galea, Managing Director at The Synapse

"We at Vivian continuously strive to work closely with local and foreign partners in healthcare to improve the quality of life of others."
Joanna Gatt, Executive Director at Vivian Corporation

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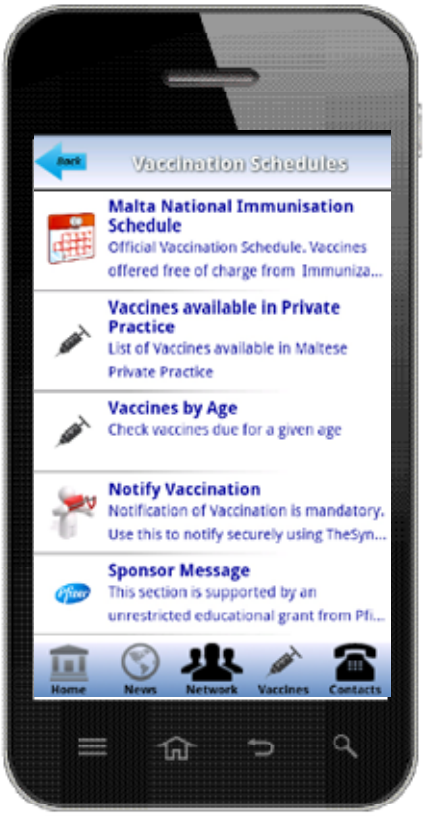

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The vaccination section of TheSynapse app is supported by an unrestricted grant by ***Pfizer***

EUROPEAN PARLIAMENT ELECTIONS – QUO VADIS?

The parties which have obtained the highest share of votes during the 2014 European Parliament elections are the Group of the European People's Party (28.36%), the Group of the Progressive Alliance of Socialists and Democrats (25.43%) and the Alliance of Liberals and Democrats for Europe (8.52%). Turn-out was only 43.09%. Obviously, this has to be taken into perspective. In Malta the two main political parties elected an equal number of representatives.

Presently the European Parliament contains 7 parties, together with numerous other non-attached MEPs which are not allied to any of the political groups. Interestingly, when compared to the last election in 2009, there was a shift of 66 MEP from the 2 main parties to the other 5 parties. In this case, one must also take into consideration the fact that, following the provisions detailed in the Lisbon Treaty, the number of MEPS has been reduced from 766 to 751.

Amidst this changing scenario, the health community will have to work harder to ensure that the four areas identified in the **Europe 2020** strategy which pertain to health are implemented in an efficient manner. These are:

- **Innovation Union** – the aim is to make Europe a world-leader in developing innovative ways to promote active and healthy ageing. This includes the improvement of the sustainability and efficiency of social and healthcare systems (a major challenge for Malta, I must say!)
- **Digital agenda for Europe** – this focuses on developing and using digital applications. This includes giving citizens an online access to their medical health data and achieve widespread telemedicine deployment.
- **Agenda for new skills and jobs** – this will help highlight the economic role of mental health of the workforce. This should result in improved working conditions which in turn will help reduce health inequalities and absenteeism. Research into the growing incidence of mental illnesses in the workplace is also being investigated.
- **European platform against poverty** – the aim is to lift at least 20 million Europeans out of poverty by 2020.

Europe consists of 500 million citizens. Maybe for the 57% who are listed on the European electoral register and who decided to not vote in the European Parliament, these arguments do not hold water. However everyone falls sick and everyone ages. So in my opinion, even if one were to consider solely the aforementioned health-specific areas, everyone should vote, irrespective of whether one considers the system to be wrong or not. Ultimately, the system is there to stay...

Cover:
Beyond global glory
by Stephen Falzon

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

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Onbrez Breezhaler (indacaterol) inhalation powder, hard capsules
PRESENTATION: Onbrez Breezhaler 150mcg and 300mcg inhalation powder hard capsules containing indacaterol maleate, and separate Onbrez Breezhaler inhaler. **INDICATIONS:** For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** Recommended dose is the inhalation of the content of one 150mcg capsule once a day, administered at the same time of the day each day, using the Onbrez Breezhaler inhaler. Dose should only be increased on medical advice. The inhalation of the content of one 300mcg capsule once a day has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. No dose adjustment required in elderly patients, for patients with mild and moderate hepatic impairment or for patients with renal impairment. No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. Onbrez Breezhaler capsules must not be swallowed. 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, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** ***Asthma:*** Onbrez breezhaler is a long acting beta2-adrenergic agonist, which is only indicated for COPD and should not be used in asthma. 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.***Paradoxical bronchospasm:*** If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. ***Deterioration of disease:*** Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. ***Systemic effects:*** Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Cardiovascular effects:*** Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. ***Hypokalaemia:*** Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. ***Hyperglycaemia:*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1 2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. ***Pregnancy and Lactation:*** No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. **INTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.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. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, , headache, , cough, , rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia ,paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 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: +356 22983217/+35621222872 2014-MT-ONB-24-Mar-2014

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ISSUE GUIDE

TheSynapse

MOIRA MIZZI

THE CHALLENGES TO HOMEOSTASIS IN THE VAGINAL ECOSYSTEM

The essence of healthy existence for every living being is homeostasis within itself and the surrounding environment. Sadly, the human being, despite being at the highest echelons of the animal kingdom, is the only living organism who continuously defies this ideology resulting in the calamitous state of affairs we are experiencing both in our environment and in our personal health, both physical and psychological.

Vaginal ailments, even though usually not so devastating, are a clear example of how loss of ecological balance can affect our quality of life. The most common of these is vaginitis, and more specifically, bacterial vaginosis.

Homeostasis in the post-pubertal human vagina is maintained by the colonization of commensal bacteria, mainly hydrogen peroxide-producing lactobacilli[1]. Other bacteria are also present, namely streptococcal species, gram-negative bacteria and other anaerobic species, including *Gardnerella vaginalis*. *Candida albicans* is also present in 10 to 25% of asymptomatic women[2].

Estrogen increases the production of glycogen in vaginal epithelial cells and its metabolism by the lactobacilli to lactic acid. This renders the vaginal ecosystem mildly acidic (pH 3.8-4.5) and inhibits the adherence of bacteria to vaginal cells; the hydrogen peroxide which is produced by the lactobacilli inhibits the growth of bacteria and has also been found to kill HIV in vitro[2]. This mutualism between lactobacilli and vaginal epithelium, together with innate and acquired immunity, protects the vagina from colonisation by pathogenic bacteria, thus preventing ascending or systemic infection[3].

The most common organisms causing vaginitis are bacteria, fungi and protozoa. Bacterial vaginosis is not caused by one agent[4], as is commonly believed but is rather a polymicrobial syndrome usually caused by *Gardnerella vaginalis, Mobilincus, Bacteroides saprophytes* and *Mycobacterium Hominus; Chlamydia trachomatis* and *Neisseria gonorrhoea* are less commonly implicated with bacterial vaginosis. Fungal vaginitis is usually caused by *Candida albicans*. The epidemiology varies according to the geographical location - bacterial vaginosis is the most common vaginal infection followed by vulvo-vaginal candidiasis in the US; in Europe however, the fungal form is the most prevalent[1].

Bacterial and fungal vaginosis usually occur following the exposure to an external agent that alters the vaginal homeostasis either by altering the pH or by disturbing the vaginal commensal flora. This could include biological factors like pregnancy and menopause or external agents such as vaginal douches, chemotherapy (direct inhibition or cell lysis[5]), sexual intercourse (multiple partners) and contraception (IUD). Trichomoniasis, on the other hand, is a sexually transmitted disease caused by the protozoan *Trichomonas vaginalis*. Vaginosis is easily curable with adequate treatments; however all types can be associated with recurrent relapses and adverse outcomes, including increased risk of HIV or other forms of upper genital infections including pelvic inflammatory disease, premature rupture of membranes or abortion[1,2].

Despite there being a few lactobacillus species constituting the vaginal flora, there are various species- and strain-specific

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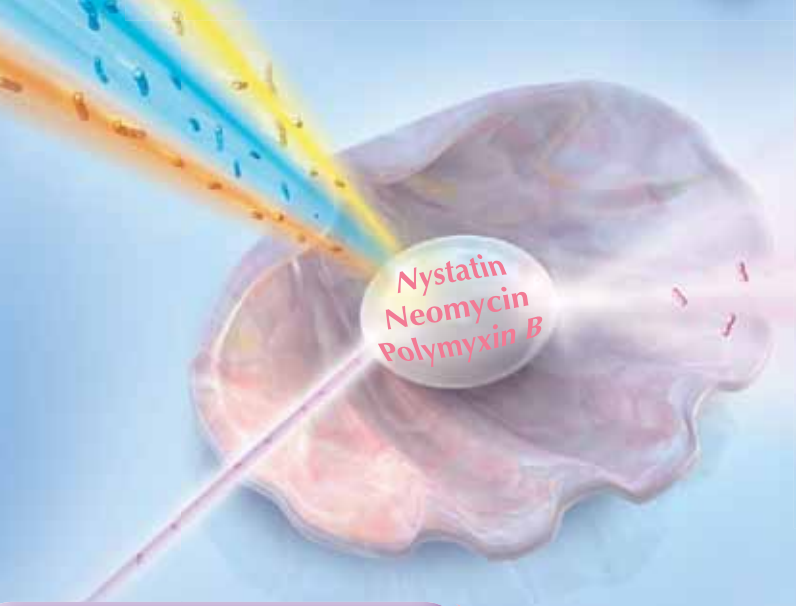

1 vaginal capsule
in the evening for 12 days

LOCAL TREATMENT ➤ **Vaginitis due to sensitive germs and non-specific vaginitis[3]**

POLYGYNAX®, vaginal capsule. **COMPOSITION:** neomycin sulphate 35 000 IU, polymyxin B sulphate 35 000 IU, nystatin 100 000 IU. **THERAPEUTIC INDICATIONS:** local treatment of vaginitis due to sensitive germs and treatment of non-specific vaginitis. The official recommendations concerning appropriate use of antibacterial products must be taken into consideration. **POSOLOGY AND METHOD OF ADMINISTRATION:** for adults only. One vaginal capsule in the evening at bedtime for 12 days. Advice: treatment is associated with hygiene recommendations (put on cotton underwear, avoid vaginal washing, avoid using an internal tampon during treatment...) and elimination of initiating factors as much as possible. Treating the partner must be discussed for each individual case. Do not stop the treatment during menstruation period. **CONTRAINDICATIONS:** this drug is contraindicated in the following situations: hypersensitivity to one of the components (or relevant group sensitivity). Use of a diaphragm and latex condoms. This treatment is generally not recommended for use with spermicides. **WARNINGS*:** treatment should be interrupted in the event of local intolerance or allergic reaction. **PRECAUTIONS*:** the duration of treatment should be limited because of risk of selecting resistant strains, leading to secondary infection. **INTERACTIONS WITH OTHER DRUGS AND OTHER INTERACTIONS:** Contraindicated combination: + condoms: risk of rupture. Unsuitable combination: + spermicides: local therapy can stop the action of a spermicidal local contraceptive. **PREGNANCY:** there is no available reliable data concerning teratogenesis in animal species. Clinically, no malformative or foetotoxic effect has been reported. Nevertheless, monitoring pregnancies exposed to this drug is not enough to exclude all risk. Consequently, POLYGYNAX® is not recommended for use during pregnancy. **LACTATION:** due to the lack of data on the drug's passage into maternal milk, it should not be used during breast-feeding. **UNDESIRABLE EFFECTS:** possibly contact allergic eczema. This occurs more frequently in long-term use. These lesions may spread far from the treated areas. Due to the presence of soybean oil, risk of hypersensitivity reaction (anaphylactic shock, urticaria). Possible systemic toxic effects (renal, hearing,...) is limited due to recommended short-term treatment. **PHARMACODYNAMIC PROPERTIES*:** local anti-infectious drug (G. genitourinary system and sexual hormones). Combination of neomycin, polymyxin B and nystatin. Neomycin is an aminoside antibiotic. Polymyxin B is a polypeptide antibiotic. Nystatin is a fungicide against Candida. **SPECIAL STORAGE PRECAUTIONS:** store at a temperature not exceeding 25°C. **PHARMACEUTICAL FORMS AND PRESENTATIONS:** box of 6 & 12 vaginal capsules under blister (PVC/Aluminium). **TEXT REVISION DATE:** April 2010. ***For more additional and complete information, please consult the Summary of Product Characteristics.**

(1) Serov V N. Using Polygynax® to treat non-specific bacterial and fungal vaginitis. Russian Gyneco-Obstetrician Journal Association. 2001;1:64-67.
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(3) Summary of product characteristics (SPC) Polygynax® revised in july 2008.

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differences which account for the wide variability in their ability to maintain the stability of the vaginal ecosystem. Thus, the vaginal immunity is one of the factors - apart from the effect of endocrinal changes on vaginal physiology, and external challenges - in determining both the liability to infection and recurrence, as well as the propensity to respond to treatment[3].

Diagnosis hinges on the symptomatology described by the patient and the naked eye examination of the vaginal discharge. The clinical findings can be very similar especially in the bacterial and fungal cases which can render diagnosis difficult. Microscopical assessment of the discharge is the mainstay of diagnosis; unfortunately it is usually resorted to on therapeutic failure of the usual repeated courses of empirical therapy; this not only leads to a financial and social burden resulting in non-compliance on the part of the patients but also contributes to the overall emergence of resistance[1].

The hallmark of the management of vaginitis rests on the triad of prevention, education and antimicrobial treatment, all of which lie in the remit of the general practitioner. Education so far is mostly carried out through face-to-face interventions when the patient turns up for treatment of one or more of the unpleasant symptoms, or for the insertion of a contraceptive device. The success of prevention is directly proportional to how much the educational messages manage to get driven home and how much the patient truly comprehends and appreciates their importance especially considering the embarrassment associated with such disturbances.

Antimicrobial treatment comes mostly in the form of topical agents - creams or pessaries - or oral medication. Creams or pessaries can deliver either one antimicrobial agent or contain a synergistic combination of two or more active ingredients to increase the likelihood of remission and decrease the risk of recurrence.

Unfortunately, recurrence of vaginal infections is common. In most cases this is the result of wrong diagnosis, self-treatment with over-the-counter medication, poor compliance to treatment by the female, failure to treat the male partner, resistance to treatment and/or non-adherence to the preventive measures advised. The rest of the recurrences occur due to an inherent predisposition of the female, either as a result of a particular physiological state e.g. pregnancy and menopause, the presence of an IUD, insufficient numbers of peroxide-producing vaginal lactobacilli or altered host immune response[3].

The best way to avoid this state of affairs is to take a structured and systematic approach to the management of vaginitis. A good history from the patient regarding symptomatology, past medical history and sexual/gynae history is an important start. This should be ideally followed by pelvic examination including determination of vaginal pH, visual assessment and microscopic evaluation of the discharge[2]. It is only through correct diagnosis that recurrence of disease and misuse of medication can be avoided. In this day and age, where vaginal and sexually transmitted diseases are exponentially increasing due to our 'boundary-less' way of living, the author strongly believes that prevention, especially through 'out there' education, should be given more importance and validity. The path to achieving a balance is simple… the difficulty lies in choosing it.

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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

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IMPROVING PATIENT ACCESS TO INNOVATIVE MEDICINES -

THE FRAMEWORK IN WHICH DIFFERENTIATED PRICING MAY OFFER A SOLUTION

OBJECTIVE

The research-based pharmaceutical industry considers that price differentiation between EU Member States could greatly improve affordable patient access to innovative medicines in those markets where there is a significant access problem. Adapting prices of pharmaceuticals to reflect the ability to pay in different geographical or even socio-economic segments can offer a win-win situation in terms of generating dynamic efficiencies that contribute to both the sustainability of healthcare systems and the pace of innovation. Yet today's pricing and reimbursement practices have the effect of discouraging price differentiation. Member State action and support from the European Union are required to create a framework to enable and encourage voluntary recourse to differentiated pricing.

EFPIA calls for:

- Member States to take reasonable measures to facilitate the introduction of effective differentiated pricing policies that reflect variations in ability to pay at national level. The need for greater solidarity in tackling growing health inequalities in Europe means that there are a number of preconditions to the successful introduction of differentiated pricing:
  1. any scheme should be the result of bilateral voluntary arrangements at a national level that protect the confidentiality of the net pricing agreed
  2. international reference pricing schemes should be founded on best practices to ensure that they consistently compare 'like with like' and exclude extraordinary cost containment measures
  3. Member States should take the necessary steps to ensure that medicines specifically priced for patient groups who would not otherwise be able to afford themare delivered to those patients and are not otherwise diverted
- Provided these preconditions are satisfied, the Commission could usefully support the piloting of measures enabling differentiated pricing in a selection of countries where access is particularly poor or where the institutional framework readily permits such measures
- A broader debate is required at EU level to ensure that the impact of national price controls is limited to the national territory (as articulated in Recommendation VI of the 2002 G10 Medicines Report and in Recommendation 9.2 of the Final Report of the High Level Pharmaceutical Forum), for example, to allow for market-based pricing for products other than those actually dispensed and reimbursed through public funding.

THE PROBLEM

Adapting prices of pharmaceuticals to the purchasing power of patients and consumers in different geographical or socio-economic segments can improve access to and affordability of life-saving medicines in both the short and long term. It can be effective as part of broader efforts to ensure that healthcare systems are sustainable. It is relevant in the European context where the gaps between GDP and healthcare spend per capita and access to the latest innovative medicines have been widening and are significant.

Economic literature has long recognised that differentiated pricing reflecting ability to pay, referred to as "Ramsey pricing", provides the highest social benefit to consumers while generating sufficient revenues to cover the continued financing of the high risk, long term innovation cycle required to bring new medicines to market.

Yet the main obstacle to benefiting from the efficiencies arising from differentiated pricing is the threat of trade diversion from low priced to high priced countries.[1] According to OECD, differentiated pricing is "*…increasingly not possible in an era of freer trade and external price referencing. This may well result in problems in the availability and affordability of some medicines in some countries, both within and particularly outside the OECD, unless policy makers change pricing and reimbursement policies to adapt to the new market dynamic.*"[2]

Europe-wide solidarity is required in order for differentiated pricing to be a potential solution to growing health inequalities. Ramsey pricing implies that wealthier nations are willing to pay a price reflecting the value of innovative medicines and resist the short-term static gains to be had from arbitrage or referencing low price markets. At the same time, patients and healthcare systems in poorer countries have access to medicines specifically priced for patient groups who would not otherwise be able to afford them. Low priced medicines specifically provided for these markets should not be diverted to more affluent populations for which they were not intended.

The merits of differentiated pricing as well as the drawbacks of international reference pricing have been debated in various discussion platforms involving patients, public health officials, EU and national policy makers, stakeholders and industry. Discussion platforms include *inter alia*:

- The G10 and the High Level Pharmaceutical Forum that each recommended the adoption of the principle of non-extraterritoriality of national price controls invited the Commission and the Member States to "*secure the principle that a Member State's authority to regulate prices in the EU*

should extend only to those medicines purchased by, or reimbursed by the state"[3]

- The Tajani 'Access to Medicines in Europe' Working Groups (Small Markets, Managed Entry Agreements, Orphans) have made strong recommendations to explore the concept of differentiated pricing in order to improve access in small markets
- The EPSCO reflection process under the Working Party on Public Health at Senior Level (sub-group on the cost effective use of medicines led by The Netherlands) has lead to a study being commissioned by DG SANCO from Creativ-ceutical on the impact of external reference pricing (to be released in early 2014)
- The Belgian government has expressed willingness to follow through on the December 2010 Health Council conclusions adopted under the Belgian Presidency to examine approaches to facilitate access to valuable innovative medicines throughout the EU: see the non-paper on differential pricing presented at the July 2013 Informal Health / EPSCO Council
- Strong advocacy by some patient organisations, in particular EURORDIS (orphans).

The time is ripe for action.

POLICY PRINCIPLES FOR THE ESTABLISHMENT OF A FRAMEWORK ALLOWING DIFFERENTIATED PRICING

To be effective in ensuring broader access to patients, any differentiated pricing proposal must reflect the following basic principles.

1. NET PRICING AGREEMENTS MUST REMAIN CONFIDENTIAL

Differentiated prices cannot be achieved by formulaic determinations but by decentralised negotiations between pharmaceutical manufacturers and healthcare systems. For differentiated pricing to be feasible in Europe for as long as Member States retain international reference pricing, it is essential that discounts, rebates or price volume agreements and other contract terms (such as claw back mechanisms, risk sharing agreements and managed entry schemes) are not disclosed. They are a normal feature of most commercial transactions. Protecting their confidentiality offers a stop-gap rather than a sustainable long-term solution, but they are nonetheless important in order to facilitate the differentiation of sales prices according to a purchaser's ability to pay.

The Transparency Directive does not require transparency of net prices actually paid. Requiring such disclosure would risk a convergence of price levels within a narrower band than exists today.

2. DIFFERENTIATION BETWEEN MEMBER STATES MUST REFLECT ECONOMIC REALITY

In order to achieve affordability and more equal access to healthcare in Europe in the short term, Member States should encourage voluntary differentiated pricing arrangements that reflect different demand conditions in any given national market, including, but not limited to, the ability to pay.

3. MEMBER STATES MUST RETHINK INTERNATIONAL REFERENCE PRICING SCHEMES

Pricing and reimbursement decisions ought to balance affordability and value in each market. Whilst the Transparency Directive requires pricing to be objective, international price referencing is not an objective system. It has significant distortive effects within and beyond Europe, effectively importing budgetary considerations from other markets that are at different levels of economic development.

Member States should revisit their respective reference schemes to build in more objectivity and explicitly recognise the benefits of greater solidarity in achieving equal access to healthcare. How this is implemented can vary from one country to another but, unless and until this issue is addressed, differential pricing is unlikely to be effective.

The distortions created by international reference pricing can at least be minimised if price regulation is limited to reimbursable products and a number of guiding principles are applied. Competent authorities should compare prices of similar countries with similar wealth but also similar epidemiology, similar medical practice and/or similar health priorities. They should rely on the average price in similar countries and not the lowest and compare 'like with like' (for instance, by comparing cost per day of therapy, by taking into consideration the different distribution margins or tax regimes in order to compare prices at similar (ex factory) levels. They should acknowledge, at a minimum, that emergency price reductions in countries worst affected by the economic crisis should not be used as reference prices for the determination of prices or reimbursement levels of medicinal products in other countries.

4. MEMBER STATES SHOULD ACT WITHIN THEIR PRICING DISCRETION TO ENSURE BETTER ACCESS FOR PATIENTS

Member States must fully avail of their competencies to ensure better access and patient welfare. They are entitled to ensure that the impact of national price controls is limited to the national market, for example, by allowing market-based pricing for products not actually dispensed and reimbursed through public funding. They are equally entitled to foresee measures to ensure security of supplies.[4]

1. See Implications of international reference pricing and parallel trade on social welfare and patient access, CRA, September 2012.
2. OECD (2008), Pharmaceutical Pricing Policies in a Global Market, p. 205
3. According to the High-Level Pharmaceutical Forum's Final Report of October 2008: "…It has also become clear that affordability has a European dimension. A similar price-level leads to a different level of affordability depending on the economic situation of each Member State. Attention could be given to measures that allow companies to offer medicines at affordable prices in each EU market. Limiting price-control only to nationally used volumes, as Recommendation 6 of the G-10 Medicines report stipulates, would allow differential pricing taking account of national socio-economic indicators like GDP-levels." The Commission's Communication on Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector also recognises that similar price levels can lead to different levels of affordability. COM(2008) 666 final, December 2008. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0666:FIN:en:PDF
4. For example, Article 36 of the Treaty on the Functioning of the EU offers a short-term solution for Member States to impose limited and proportionate export bans in response to real shortages that pose a serious risk to public health. Recourse to Article 36 does not address the fundamental malaise of today's inequality of access to innovative medicines.

GLENN PAUL ABELA
PAUL CALLEJA

GENERAL ANAESTHESIA IN ACUTE INTERMITTENT PORPHYRIA

ABSTRACT

Acute intermittent porphyria (AIP) is caused by the deficiency of porphobilinogen deaminase, a haem synthesis enzyme, giving rise to crises characterized by abdominal pain, tachyarrythmias and psychiatric features[1-3]. Anaesthesia in AIP is challenging because it has to avoid precipitating an attack[1,3]. We report a case of a lady with AIP who underwent total abdominal hysterctomy whose anaesthesia was uneventful.

INTRODUCTION

Acute intermittent porphyria (AIP) is a type of acute porphyria caused by the deficiency of porphobilinogen deaminase, an enzyme involved in haem synthesis[1]. It may give rise to acute crises characterized by severe abdominal pain (but no signs of peritonism), muscle weakness, tachyarrythmias and psychiatric features[1-3]. Administration of anaesthesia may be challenging in that it requires a detailed preoperative assessment and a careful selection of safe drugs in order to avoid the precipitation of an attack during an already physiologically-stressful time[1,3]. We here present the case of a lady with known AIP who underwent major gynaecological surgery and whose anaesthesia was uneventful.

CASE REPORT

A 42 year old female, a known case of AIP, was scheduled for elective total abdominal hysterectomy with conservation of the ovaries. She was reviewed at the preoperative assessment clinic two weeks before the operation. She had been diagnosed with AIP at 14 years and had been in remission for the previous seven years. Other than this she had no other medical co-morbidities, was on no regular medications and had no known allergies. Physical examination was unremarkable. There were no indications of a difficult intubation. Preoperative blood tests (full blood count, renal profile and coagulation screen) were within normal limits. A chest radiograph was clear and an electrocardiogram was in sinus rhythm.

The patient was admitted a day before the surgery, was requested to refrain from any oral intake for eight hours prior the procedure and was placed first on the operating list. She was premedicated with 2mg of midazolam on arrival to the anaesthetic suite and an epidural catheter was inserted at L3/L4 for intra- and postoperative pain control. Anaesthesia was induced using 180mg of propofol and 100mcg of fentanyl and maintained using desflurane, oxygen and medical air. Muscle relaxation was achieved using 30mg of atracurium. The patient was intubated and mechanically ventilated with a target $ETCO_2$ of 30 to 35mmHg.

Intraoperatively, she was administered intravenous paracetamol (1g) and ondansetron (4mg) and two boluses of bupivacaine (12.5mg) with fentanyl (12.5mcg) epidurally. The fluid regime involved 2L of Hartmann's solutions and 400mL of 10% dextrose. Monitoring was non-invasive and included blood pressure readings, pulse oximetry, cardiac rhythm and capnography. She was mildly hypotensive for the first half an hour from induction, with the lowest recorded blood pressure value of 70/40, but this normalized with two phenylephrine boluses of 100mcg each.

Arterial blood gases and electrolyte measurement taken one hour into the surgery revealed a normal acid-base status but a potassium of 3.13mmol/L and a glucose of 16.8mmol/L. Potassium was supplemented to the Hartmann's solution (5mL of 20% KCl in 1L of Hartmann's) and the 10% dextrose was stopped.

The operation was completed successfully and emergence from anaesthesia was routine. In the recovery area, the patient was administered 12.5mg of prochlorperazine intramuscularly and another two boluses of epidural bupivacaine and fentanyl. A second blood test showed a potassium of 3.51mmol/L and a glucose of 8mmol/L. She was transferred to the ward once she was fully conscious and with the pain controlled.

The postoperative period was without any complications. The fluid prescription was of 1L of 5% dextrose and 2L of Hartmann's (with potassium added accordingly) per day.

PORPHYRIAS ARISE FROM ENZYME DEFICIENCIES IN HAEM BIOSYNTHESIS RESULTING IN A PARTIAL BLOCK OF THE CASCADE AND THE ACCUMULATION OF THE PORPHYRINS

Oral intake was started six hours after the surgery and the intravenous infusion was discontinued once this was re-established. The epidural was removed after 24 hours because of the patient's concern over a moderate sensory deficit in the right upper thigh. Analgesia was then achieved with regular intravenous paracetamol and as required, intramuscular pethidine.

She was discharged after four nights in hospital.

DISCUSSION

PORPHYRIAS

Porphyrias are diseases of haem synthesis specifically involving the constitutent porphyrins. Porphyrins are cyclic molecules capable of forming complexes with several metals such as iron. The combination with the latter allows for the formation of haem and consequently of essential structures such as haemoglobin, myoglobin and the cytochromes[1]. Haem is procuded by a cascade of enzyme-mediated reactions principally under the control of aminolevulinic acid (ALA) synthetase which in turn depends on the level of haem in a negative feedback mechanism[1,2].

Porphyrias arise from enzyme deficiencies in haem biosynthesis resulting in a partial block of the cascade and the accumulation of the porphyrins[1,3]. They can be classified either by the site of porphyrin overproduction (hepatic or eythropoietic) or in terms of presentation (acute or non-acute). The latter is the most useful and it includes four types of porphyrias: acute intermittent, variegate, hereditary coproporphyria and plumboporphyria[1,2]. They are commoner in women and in the third and fourth decades of life[1].

AIP is the commonest of the acute forms and results from low levels of the porphobilinogen deaminase enzyme encoded on chromosome 11q24. It is inherited in an autosomal dominant fashion with incomplete penetrance[2,4]. Patients have a good prognosis once diagnosed, however, AIP gives rise to the severest presentation and is the most likely to be fatal in an acute attack[1,2]. Such an event is precipitated by an increase in the demand for the haem molecule and this typically occurs with the activation of the hepatic cytochrome P450 in starvation, dehydration, infection, hormone fluctuations and the administration of drugs which require this enzyme for their metabolism[1,3]. Patients thus have inadequate haem production, increased ALA synthetase activity and a widespread build-up of porphyrins[2].

An acute event varies from a mild attack to a life-threatening neurovisceral crisis. The commonest feature is severe abdominal pain with little or no clinical signs and is accompanied by nausea, vomiting and occasionally diarrhoea. There may be muscle weakness (proximal more than distal, and in upper limbs rather than lower) which may progress to quadriparesis and respiratory failure. Cardiovascular features include tachycardia, arrhythmias and hypertension and these are characteristic of autonomic disturbance. Psychiatric problems are also intimated and these range from mood disturbance and confusion to full-blown psychosis[1-3].

Diagnosis of AIP requires the detection of increased ALA, porphyrins and their precursors (particularly porphobilinogen) in urine[1].

AIP AND ANAESTHESIA

AIP represents an anaesthetic challenge because of the careful selection of drugs necessary[1,2]. Certain agents in routine use, such as thiopentone, sevoflurane, dexamethasone, non-steroidals and ephedrine are described as unsafe in AIP and should be avoided[3].

We induced anaesthesia with drugs that have long been listed as safe in porphyric patients (propofol and fentanyl), but maintained it with desflurane which, although its use in AIP has been documented for some time, has been included in the safe drugs list for porphyrias only recently[5,6]. This case thus further exemplifies the safety of desflurane in AIP.

We administered ondansetron and prochlorperazine as antiemetics and established analgesia with intravenous paracetamol and epidural bupivacaine and fetanyl. Vasopressor support was provided using phenylephrine, which is metabolised by the liver monamine oxidase[7]. Ephedrine was avoided since it induces ALA synthetase and cytochrome P450 and thus its use risks precipitating an AIP attack[8].

This case also highlights the importance of close monitoring of the patient's intraoperative metabolic status. Earlier and more frequent blood analysis could have allowed for tighter glycaemic and electrolyte control. This is essential to minimize the physiological stressors associated with surgery, and should also include the shortening of the preoperative starving period and the use of dextrose in intravenous infusion regimes[3].

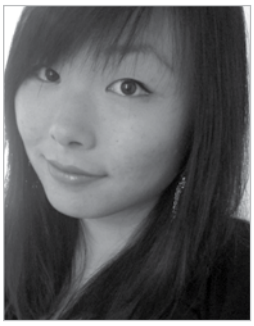
REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

YIMENG ZHANG

A DAY IN THE LIFE OF A ... PHYSIOTHERAPY STUDENT

During my training to become a physiotherapist, I was fortunate to experience large varieties of situations and meet diverse groups of people. However, an encounter with one particular patient left an impact on me; surprisingly, it was one I had limited interactions with. This patient was an elderly woman suffering from a chest infection in a geriatric ward. She was referred to me to help to improve her mobilisation and eventually go home. When I first met her she seemed frail and spoke weakly, whenever she tried. Over the weeks, she made minimal progress and was still unable to get off the bed. One day, I was informed that her chest infection was getting worse as she was unable to swallow her drinks since some fluids were entering her lungs. A speech and language therapist was sent to help her and as a student, I was allowed to go along and learn from this experience. The patient was given a fluid thickener. Unsurprisingly, the patient refused to drink it and with her frail voice, begged to take normal drinks again. After half an hour of convincing, she was giving the ultimatum, "would you rather take this drink or harm your body and die?" Hearing this, she held the drink closer to her side as a silent way of agreeing. Having done our jobs, we left. That was the last time I heard of her. One day, curiosity led me to ask regarding her progress, expecting to hear that her chest is better. Instead I was told that she had passed away a week after our last encounter. It is not rare to have patients pass away, especially on the geriatric ward; however, I felt an overwhelming sense of sadness. She made an impossible choice between quality of life and living life itself. Sometimes I wonder, if she could have seen the future, would she have decided otherwise?

MMSA



MATTHEW ZARB

THE NEWLY-ELECTED EXECUTIVE TEAM

MPSA

Greetings Synapse readers! The newly-elected Executive Team representing the Malta Pharmaceutical Students' Association (MPSA) has recently (as of March) started its 2014-15 term in office.

MPSA wishes to thank the previous Executive Team, which organised numerous health campaigns in the past year through hard work and commitment, during which considerable awareness was raised thanks to the great response from the general public. One can surely mention World Osteoporosis Day, World Diabetes Day and World Pharmacy Week as a few prime examples in this regard.

Not only does the new Executive Team wish to continue in the former's footsteps, but MPSA has also set out on a new goal: that of extending its reach to collaborate with other registered organisations representing students on campus, at any given opportunity. We believe this to be a fundamental step in helping our organisation to grow not only in a recognition sense, but also through forging friendly and professional relations with students from other courses.

As a testimony to this, the new MPSA Executive Team inaugurated its 2014-15 calendar of events by collaborating with GħSL (Għaqda Studenti tal-Liġi) and TSA (Tourism Studies Association) to host a get-together event for students on the 14th of April at Surfside, Sliema. Not only was the event nothing short of a success from a turnout perspective, but it further helped us in reaching our main target i.e. that of prioritising the formation of new professional acquaintances not limited to the health sector.

MPSA also took part in the fundraising walk from Bisazza Street to Spinola Bay (and back) organised by the Richmond Foundation on the 27th of April entitled: "There is no health ... without mental health!". MPSA together with MMSA (Malta Medical Students' Association) had a stand set up in Bisazza Street, which the public was encouraged to visit for free on-site BMI testing, blood pressure testing and blood glucose testing. Advice on attaining a healthier diet and lifestyle was also provided.

MPSA would like to take this opportunity to thank all the other student organisations mentioned above for their help in organising the said events, and is looking forward to future collaborations with them and other student organisations.

On a final note, I invite you to visit our Facebook page (Malta Pharmaceutical Students' Association – MPSA), which is constantly being updated so as to keep people up-to-date with the activities our association participates in, as well as those which it organises.

Till next time, happy reading!

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SEPSIS

CARL TUA

ABSTRACT

Sepsis, which may be defined as the systemic illness caused by the suspected invasion of normally sterile parts of the body by microbial organisms, is a major healthcare problem, ranking among the top ten causes of death. This article reviews the evidence behind the general and specific measures in the management of sepsis, based on the Surviving Sepsis Campaign Guidelines.

WHAT IS SEPSIS, AND WHY IS IT IMPORTANT?

Sepsis is a major healthcare problem, affecting millions of people worldwide, occurring at all ages and in different patient groups, from healthy individuals in the community to ill hospitalized patients.[1] Sepsis may be defined as the systemic illness caused by the suspected invasion of normally sterile parts of the body by microbial organisms. Sepsis leading to acute organ dysfunction or tissue hypoperfusion is defined as severe sepsis, and severe sepsis resulting in hypotension not reversed with fluid resuscitation is septic shock. This definition of sepsis specifically distinguishes it from the similar clinical picture of systemic inflammatory response syndrome (SIRS) that arises without an underlying infection but secondary to, for example, pancreatitis and anaphylaxis. The similarity of these syndromes is due to the same underlying deleterious host response resulting in the same pathophysiological pathways and release of cytokines and other inflammatory peptides.[2]

THE PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF SEPSIS: FROM PATHOGEN ENTRY TO SEPTIC SHOCK

The first barrier to infection is the continuous membrane of the skin, and the internal mucous membranes of the respiratory, genitourinary and gastrointestinal tract. Loss of integrity may be obvious as in the case of severe burns, or an anastomotic leak following surgery, but it may also be subtle as in the case of an insect bite. In a hospital environment such loss of integrity is often due to the use of intravenous cannulas, catheters, drains and other devices. Once an organism has gained entry, it prompts a regional immune response mediated by various cellular, cytokine and other inflammatory peptide-controlled mechanisms. The release of these effector peptides such as TNF-α, interleukins and prostaglandins results in a cascade of regional, followed by a systemic, inflammatory response. Clinically, this inflammatory response results in the clinical features and presentation of sepsis. The features of this response are very variable as it is a combination of organism virulence and burden, together with the host response factors.

The diagnostic criteria for sepsis is therefore documented as suspected infection together with some of the following features which characterize a systemic inflammatory response.

A. GENERAL VARIABLES:

- Fever >38°C
- Hypothermia <36°C
- Heart rate >90/min
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance
- Hyperglycemia i.e. >7.7 mmol/L in the absence of pre-existing diabetes

B. INFLAMMATORY VARIABLES:

- Leukocytosis i.e. WBC count >12,000 μL^{-1}
- Leukopenia i.e. WBC count <4000 μL^{-1}
- Normal WBC count with greater than 10% immature forms
- Raised C-reactive protein
- Raised procalcitonin

C. TISSUE HYPOPERFUSION

- Raised lactate
- Decreased capillary refill time i.e. <2seconds

These criteria are based on the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Levy et al specifically point that rather than giving a specific number of criteria that must be reached, "The use of the word "some" reflects the clinical reality at the bedside, rather than an arbitrary list invented for the purpose of clinical trial entry criteria". Sepsis accompanied by evidence of acute organ dysfunction or tissue hypoperfusion is defined as severe sepsis. Examples of acute organ dysfunction include decreased urine output despite adequate fluid resuscitation, coagulopathy, raised bilirubin and acute lung injury. Sepsis accompanied by a systolic blood pressure (SBP) < 90 mm Hg, SBP decrease > 40mm Hg or the need for vasopressors in the absence of other causes of hypotension and despite adequate fluid resuscitation is known as septic shock.[3-5]

MANAGING SEPSIS – GENERAL & SPECIFIC MEASURES

A. GENERAL MEASURES

i. Fluids & monitoring

Initial resuscitation should be protocolized, quantitative, and started as soon as tissue hypoperfusion is recognized. Whether crystalloids or colloids are better for resuscitation remains a much debated, but unresolved question. The "Surviving Sepsis Campaign – Guidelines" (SSCG) recommend the use of crystalloids based on the absence of any clear benefit from colloids together with the expense associated with colloid solutions. Human albuminis now rarely used following a Cochrane meta-analysis showing an excess mortality associated with its use.[6]

During the first six hours of resuscitation the goals of therapy should be:

- Central Venous Pressure (CVP) 8-12mm Hg
- Mean Arterial Pressure (MAP) >65 mm Hg
- Urine output >0.5ml/kg/hr
- Superior vena cava oxygenation saturation 70%

These end points are based on a randomized single-centre

study, which showed improved survival with targeting of these goals.[7] This "early goal-directed therapy" strategy also showed improved survival in a multicentre trial in China.[8] New methods for measuring the adequacy of fluid resuscitation such as esophageal Doppler, pulse contour analysis, and stroke volume variation in ventilated patients are used in some centers, but clinical endpoints remain useful: blood pressure, heart rate, lactate, base deficit, urine output, mixed venous saturation and central venous pressure. Pulmonary artery catheters have been shown to result in neither harm, nor benefit.[9]

ii. **Vasopressors**

Vasopressor therapy is required to maintain tissue perfusion and should be started even when hypovolemia has not yet been resolved. SSCG recommend that vasopressor therapy should target a mean arterial pressure (MAP) of 65mmHg; they also recommend norepinephrine as the first choice of vasopressor, with epinephrine being added if an additional agent is required. The use of Dopamine as a vasopressor was previously widespread, however modern advice is that Dopamine should be used only in highly selected patients i.e. those with a relative bradycardia and at low risk fortachyarrhythmias.[4,10]

iii. **Inotropes**

A trial of dobutamine infusion should be carried out in the presence of (a) myocardial dysfunction and low cardiac output, (b) tissue hypoperfusion despite adequate intravascular volume and arterial pressures. However large prospective trials have shown that using dobutamine to increase oxygen delivery to supranormal levels does not result in any benefit.[11]

iv. **Blood products**

In 1999 the results of the "Transfusion Requirements in Critical Care Trial" published in the New England Journal of Medicine, suggested that there is no increased mortality with a hemoglobin level of 7 to 9 g/dL, when compared with 10 to 12 g/dL. Thus, in the absence of specific circumstances such as ischemic heart disease or acute hemorrhage, the target range for red cell transfusion should be 7 to 9g/dL.[12]

B. SPECIFIC MEASURES

i. **Antimicrobials and diagnosis**

Although antimicrobial therapy should never be delayed to obtain samples, obtaining samples prior to therapy is essential in obtaining useful cultures. Two or more blood cultures should be taken. If present at least one culture should be taken through each lumen of indwelling devices. If cultures from a vascular device are positive much earlier than the peripheral cultures this suggests that the device may be the source of infection.[13] Prompt, appropriate antimicrobial therapy is the backbone of the management of sepsis. A treatment delay in hypotensive patients increases mortality by 7.6% per hour.[14] Even without shock there is a lot of evidence supporting giving early antibiotics.[15] The SSCG identify starting intravenous antimicrobials within the first hour of recognition of or severe sepsis or septic shock as one of the goals of therapy.

ii. **Corticosteroids**

A French multicenter randomized controlled trial showed that hydrocortisone therapy in vasopressor-unresponsive septic shock resulted in significant shock reversal and reduction in mortality in patients with relative adrenal insufficiency.[16] The CORTICUS trial enrolled patients without sustained shock, and in these patients hydrocortisone did not result in decreased mortality.[17] On this basis the SSCG recommend intravenous hydrocortisone only in patients where fluid and vasopressor therapy fail to restore hemodynamic stability. However there is no empirical evidence to guide the cessation and duration of therapy.

PREVENTION AND EARLY RECOGNITION OF SEPSIS

Sepsis-related mortality has decreased and outcomes of sepsis have also improved with earlier identification. Reducing the time of diagnosis appears to be the key step in preventing the progression of sepsis. Screening for sepsis in Intensive Care Unit environments has been shown to decrease mortality.[18] Careful infection control practices should be instituted and include hand washing, catheter care, barrier precautions, airway management, head-of-bed elevation and subglottic suctioning.[19] The role of selective oral decontamination (SOD) and selective digestive decontamination (SDD) remain somewhat controversial. Overall, the data relating to the latter techniques show a slight reduction in ventilator-associated pneumonia, but no change to overall mortality.[20]

FUTURE THERAPIES IN SEPSIS

The high mortality in sepsis means that new therapies are always being looked at, as even small decreases in mortality will result in many lives saved. Statins are well-recognized to have anti-inflammatory properties and in murine models they have shown to prolong survival, however as yet this has not undergone any human RCT.[21] Human immunoglobulin has also been investigated as a therapy in sepsis. The concept is that anti-endotoxin antibody cross reactivity will reduce the inflammatory response. However one meta-analysis concluded that, as yet, there is insufficient evidence for intravenous immunoglobulin to be used outside trials.[22] Other inflammatory response mediators include the high-mobility group box protein 1 (HMGB-1) protein that acts as a transcriptional cofactor and has a potent inflammatory cascade effect in sepsis. In rodent models, antagonism of HMGB-1 improves mortality. Ethyl pyruvate has been shown to suppress these abnormal biochemical markers including HMGB-1, and may therefore have a role in the treatment of sepsis. Ethyl pyruvate has undergone phase 2 clinical trials in patients undergoing cardiopulmonary bypass, but no results have yet been published.[23]

CONCLUSION

While exciting new therapies are being developed, sepsis care bundles, such as those introduced by the Surviving Sepsis Campaign Guidelines, remind us that the key to reducing mortality remains good clinical judgment with early diagnosis, taking appropriate samples preceding broad-spectrum antibiotic treatment tailored by local protocols, and aggressive circulatory support.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

New modalities FOR CANCER THERAPY

MAURICE CAUCHI

The classical ways of combating cancer have included surgery, radiotherapy, and chemotherapy. More recently, immunotherapy has been added to this armamentarium on the premise that cancer cells differ antigenically from normal cells, and therefore can become the target of immune cells or specifically (mono-clonally) engineered antibodies.

Apart from surgery, which aims to remove as much of the tumour as technically possible, all other therapies assume that tumour cells are destroyed preferentially compared to normal tissue, that is, the therapeutic ratio is acceptable, and that in spite of side effects, which can often be not inconsiderable, the benefits derived from these therapies are significant.

An enormous amount of work has gone into understanding the genetic structure of tumours with a view to determine what factors control tumour growth. It is now well known that genes can be turned on or off depending on circumstances. Switching on tumour stimulating genes or alternatively switching off tumour suppressing genes could result in tumour formation. This gives hope for future control of tumour growth.

Another approach, particularly in the field of leukaemias, has been the search for factors that control bone-marrow derived cell multiplication. Factors like GM-CSF have been used to coax leukaemia cells to behave more like normal bone-marrow cells and thus be modulated back to respond to normal control mechanisms.

A new approach to cancer therapy which was the subject of a recent trial report presented at the 2013 Society for Melanoma Research Congress in Philadelphia, gives hope that a new, completely different approach to cancer therapy can eventually be made available. This is based on the concept that certain viruses can specifically attack and destroy melanoma cells. The interim analysis of this phase 3 pivotal trial shows that there was significant, albeit not dramatic improvement in longevity in patients with melanoma when treated with a specifically genetically engineered virus.

This concept (referred to as 'oncolytic immunotherapy') involves the injection of a virus into patients with melanoma. The virus used for this purpose was a modified herpes simplex virus type 1, an attenuated virus which does not cause herpes, but which has the capacity to infect tumour cells, where it multiplies and eventually destroys tumour cells. This agent (referred to as T-VEC) is the first virus of this type that has been used for this purpose. Other viruses (including a coxsakie virus) are also being investigated for this purpose.

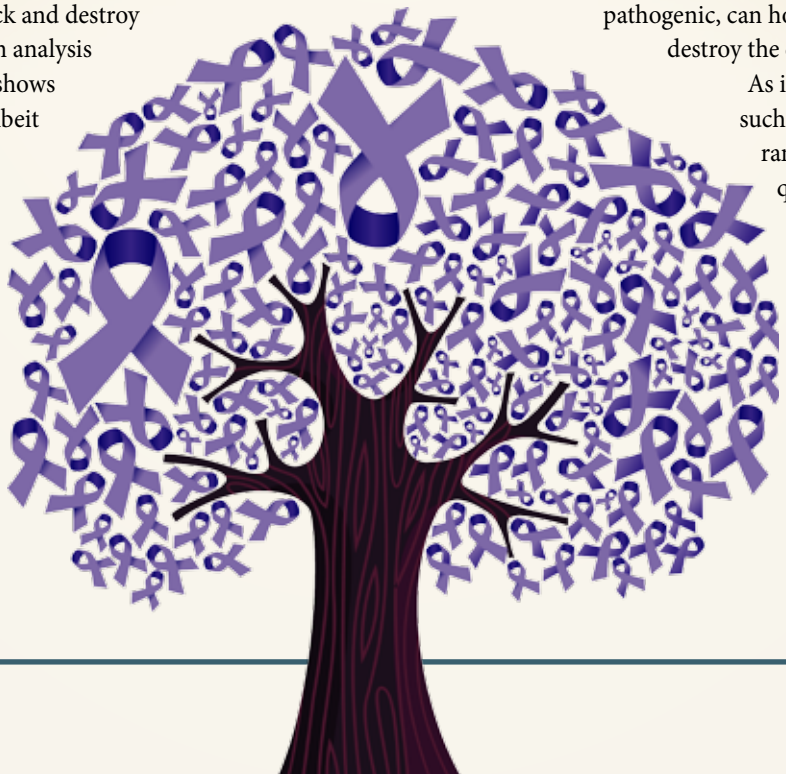
The concept that viruses show significant tropism is not new. Viruses often have a tendency to attack a specific organ. There is no doubt that certain viruses prefer to settle in, and attack preferentially certain cells (for example hepatitis viruses, human papilloma virus, viral meningitis, and lymphoma-related viruses). It is therefore quite conceivable that tumour cells are sufficiently distinct from normal parenchymal cells to be the target of specific viruses.

One must be careful not to be too optimistic about such novel modalities of therapy, particularly since, as in this case, they are still in the early stages of development.

The concept that specific viruses can attack and destroy a particular kind of cell is not new. Perhaps the most specific example of this process can be seen in the destruction of T-helper lymphocytes which are attacked by the HIV virus. In this situation, a specific virus has a particular tendency to latch onto CD4 receptors on T-helper lymphocytes and these are slowly and irretrievably destroyed. This explains the marked immune deficiency which is a hallmark of patients with AIDS.

To make use of this principle for cancer therapy, one has to identify both a specific receptor on the target cell (i.e. cancer cell), as well as ensure that a virus which is not otherwise pathogenic, can home onto these receptors to destroy the cell.

As is well known, there is no such thing as 'cancer' but a whole range of cancers which vary quite markedly from each others. It is most unlikely that receptors for viruses which present on melanoma cells can be found also on other tumours, but the results of the above investigations give a clear indication that this is a possibility.



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

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

INTERACTIONS: The co administration of Seebri Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. No clinically relevant drug interaction is expected when glycopyrronium is co administered with cimetidine or other inhibitors of organic cation transport.

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

LEGAL CATEGORY: POM

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

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

MARKETING AUHORISATION NUMBER:
Seebri Breezhaler 44 micrograms inhalation powder, hard capsules - EU/1/12/788/001-006

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 22983217/21222872

2014-MT-SBR-3-MAR-2014

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

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

Please see SPC for full prescribing information

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ALFRED GRECH
ALEXANDRA BALDACCHINO

ONCOGENE ADDICTION MIGHT BE THE ACHILLES HEEL IN CANCER - PART I

ABSTRACT

Multiple and complex genetic and epigenetic abnormalities underlie the multistage transformation of normal cells into cancerous ones. Among these abnormalities are the activation of oncogenes and loss of function of tumour suppressor genes. Besides these abnormalities, it is becoming evident that specific cancers are dependent on one or a few genes for their malignant phenotype, and this could be their 'Achilles heel'. This survival dependency of cancer cells on an activated oncogene or inactivation of tumour suppressor gene is called 'oncogene addiction' and may well be a potential way to provide more rational molecular targeted therapy. This strategy needs to integrate new approaches into the clinical setting in order to characterise the state of oncogene addiction and accordingly, apply more effective and selective anti-cancer therapies.

ONCOGENE ADDICTION: DEFINITION AND SUPPORTING EVIDENCE

Human cancer develops through a multistage process which can take decades to evolve. Such a process involves progressive accumulation of mutations and epigenetic aberrations in multiple genes.[1-4] For this reason, many cancer cells feature extensive disruptions in their genome. However, some human cancers seem to depend on one or a few genes to maintain their malignant phenotype. It is as if the cancer cells become 'addicted' to these genes and their products. Indeed, deactivating the implicated oncogene or re-activating the tumour suppressor gene can inhibit proliferation and growth of the cancer cells. Such behaviour has led to the introduction of the concept of 'oncogene addiction', first described by Weinstein et al. in 1997.[1]

Since then, several research papers have supported the role of oncogene addiction in the proliferation and survival of different types of cancer cells. Supporting evidence emerged mostly from studies carried out using (i) human cancer cell lines, (ii) genetically engineered mouse models of human cancer, and from (iii) clinical trials involving specific molecular targeted agents.

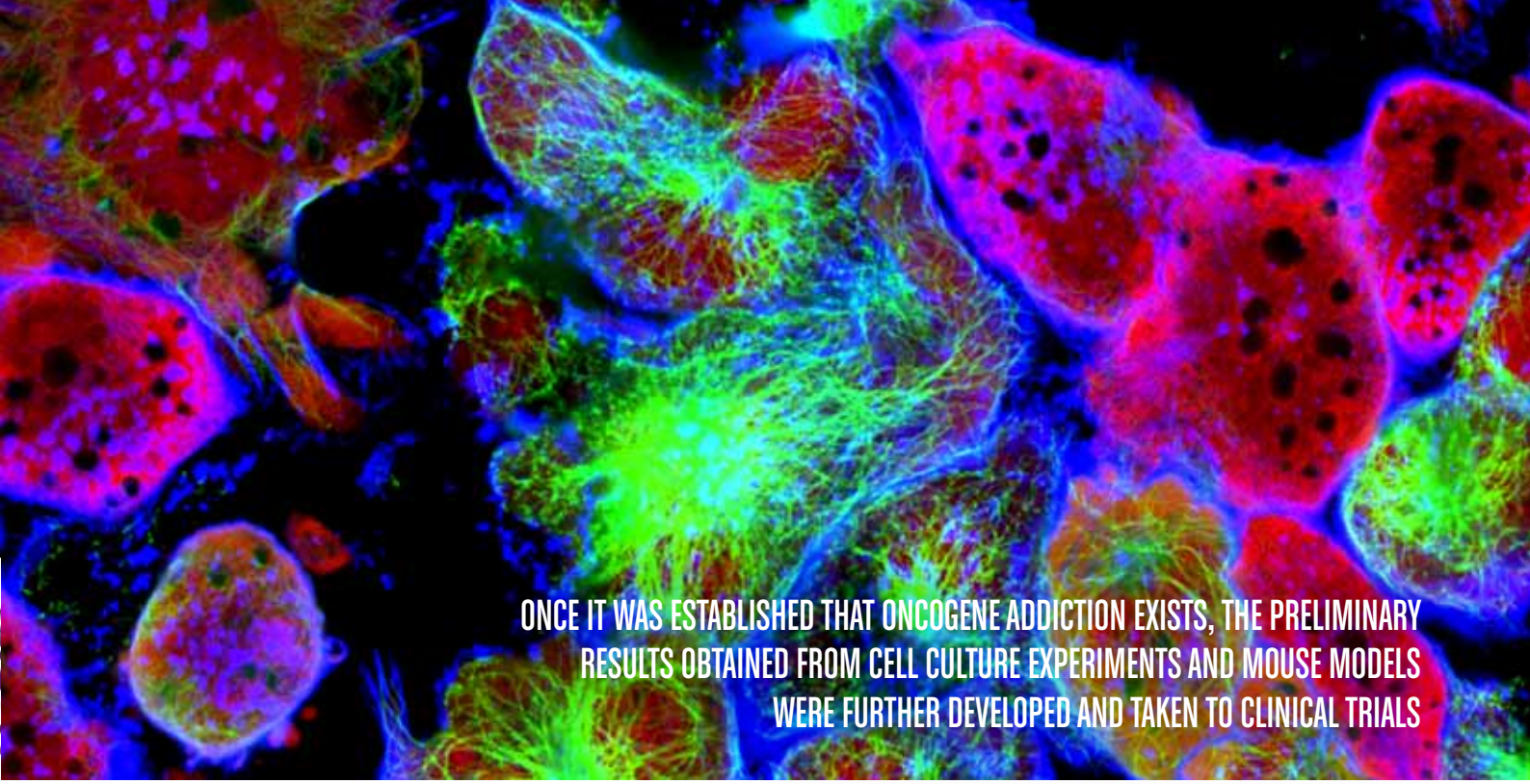
(I) STUDIES IN HUMAN CANCER CELL LINES

Throughout the years, established human cancer cell lines have been used as experimental models of human cancers. To address the role of oncogene addiction, some of these cell lines were treated with an antisense oligonucleotide, or an RNA interference (RNAi), directed to (and thus inhibiting) the respective oncogene. For instance, some investigations[5-7] targeted the cyclins, which play a key role in regulating the progression of cells through the phases of the cell cycle. One such investigation was carried out by Arber et al., who showed that the stable transfection of a cyclin D1 antisense construct in human colon cancer cells is associated with growth inhibition and decreased tumourigencity. Kornmann et al., who applied a similar approach, but used human pancreatic cancer cells instead, observed comparable results. Besides cyclin D1, other cyclins have also been targeted. Indeed, Li et al., through the use of a siRNA (small interfering RNA), showed that the depletion of cyclin E promotes apoptosis, and thus blocks cell proliferation, in hepatocellular carcinoma cells.

Oncogene addiction studies have targeted other oncogenes as well. For instance, Colomer et al.[8] showed that erbB-2 antisense oligonucleotides inhibit the proliferation of breast cancer cells. Similarly, inhibition of β-Catenin,[9] K-*ras*^{mut},[10] K-*ras*^{v12},[11] MITF,[12] and Mutant B-Raf,[13] all of which are involved in complex cell signalling pathways, has been shown to cause growth inhibition in other types of cancer cells.

(II) STUDIES IN GENETICALLY ENGINEERED MOUSE MODELS OF HUMAN CANCER

Further investigations into oncogene addiction have used genetically engineered mouse models of human cancer. Such models have been particularly useful when studying the *in vivo* mechanisms of oncogene addiction. Oncogenes or their products, such as *Bcr-Abl*,[14] c-*myc*,[15-18] erbB-2,[19] H-*ras*,[20] K-*ras*,[21] and Wnt-1,[22] have been targeted.



ONCE IT WAS ESTABLISHED THAT ONCOGENE ADDICTION EXISTS, THE PRELIMINARY RESULTS OBTAINED FROM CELL CULTURE EXPERIMENTS AND MOUSE MODELS WERE FURTHER DEVELOPED AND TAKEN TO CLINICAL TRIALS

For instance, Huettner et al. generated a conditional transgenic model of BCR-ABL-induced leukaemia, and discovered that this oncogene is required for both the induction and the maintenance of leukaemia. Similarly, D'Cruz et al. expressed the human c-MYC oncogene in the mammary epithelium of transgenic mice, and found that c-MYC expression results in the formation of mammary adenocarcinomas. Subsequently, when this gene was switched off, the cancer cells stopped dividing and underwent apoptosis. Other studies by Chin et al. and Jackson et al. showed that H-*ras* and K-*ras* are associated with tumour maintenance in skin and lung cancer, respectively. Together, these, and other studies, have shed more light into the concept of oncogene addiction.

(III) CLINICAL TRIALS INVOLVING SPECIFIC MOLECULAR TARGETED AGENTS

Once it was established that oncogene addiction exists, the preliminary results obtained from cell culture experiments and mouse models were further developed and taken to clinical trials. Targeted oncogenes included BCR-ABL,[23] EGFR,[24-26] HER-2,[27,28] and VEGF.[29,30]

One such clinical trial investigated the tyrosine kinase activity of BCR-ABL. Back in 1990, it was established that this kinase blocks apoptosis and triggers unregulated proliferation in chronic myeloid leukaemia (CML).[31] Thirteen years later, imatinib (Gleevec®, Novartis), a drug which blocks the tyrosine kinase activity of BCR-ABL, was successfully used in a clinical trial to treat CML.[23] Another tyrosine kinase inhibitor used in clinical trials is erlotinib,[25,26] which acts on the epidermal growth factor receptor (EGFR). EGFR is highly expressed in cancers such as non-small cell lung cancer and pancreatic cancer. Erlotinib is currently marketed in the EU as Tarceva® (Roche Registration Ltd).

In addition to small-molecule tyrosine kinase inhibitors, clinical trials have also made use of monoclonal antibodies. For instance, trastuzumab (Herceptin®) is a humanised monoclonal antibody that interferes with the human epidermal growth factor receptor (HER2) which is amplified in 25-30% of breast cancers.[27,28] Similarly, bevacizumab (Avastin®) inhibits vascular endothelial growth factor A (VEGF-A) which is a chemical signal that stimulates angiogenesis, especially in cancers such as breast and colorectal cancers. Together, these and other similar clinical trials have emphasised the 'addiction' of some cancers to one or a few genes for the maintenance of the malignant phenotype. *To be continued...*

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

ANNOUNCEMENT

GENITO-URINARY MEDICINE (GUM) TRAINING POST OPEN TO FAMILY DOCTORS AND DOCTORS WITH MRCOG

AN HST POST IN GUM WILL SHORTLY BE ADVERTISED. SUCCESSFUL COMPLETION OF GUM TRAINING PROGRAMME LEADS TO SPECIALIST STATUS IN GENITO-URINARY MEDICINE/VENEREOLOGY AND A HOSPITAL CONSULTANT OPPORTUNITY IN 4 YEARS. ELIGIBILITY FOR THIS POST INCLUDES (A) FAMILY DOCTORS WHO HAVE SUCCESSFULLY COMPLETED TRAINING IN FAMILY MEDICINE; AND (B) DOCTORS WITH A MINIMUM OF 2 YEARS EXPERIENCE IN GYNAECOLOGY AND POSSESSION OF MRCOG. THOSE INTERESTED ARE TO LOOK OUT FOR THE NEXT ROUND OF ANNOUNCEMENTS FOR HST POSTS.

KEEPING A FAMILY MEDICAL TRADITION GOING

MARIKA AZZOPARDI

For the past issues, The Synapse has focused on meeting young medical students and once again, this interview is with a medical student who incidentally, is also one of Malta's most promising footballers. Francesca Chircop is only 20 years old but her young age does not in any way stop her determination to succeed in two such challenging fields, both of which are highly competitive and male-oriented.

She meets me in a coffee shop and even before we make introductions I can tell that she is a very athletic person. "In my family there are three boys and myself, and I have played football since forever - as long as I can possibly remember. It has been one of those games I always played with my brothers. When I was five years old, I started playing in a boys' team (Hibernians F.C.), mainly because I wanted to join my brothers in the game. It was a natural progression. And I did not feel at all strange playing with other boys - for me it was a normal thing to do. I eventually joined a girls' football team at 10 years old but became quite bored of this experience since there were only two girls' teams at the time. This meant I was always playing against the same competitors - not much excitement in that! I managed to move back to a boys' team but only stayed there for one year. By that time, all the boys I played football with were growing up and at that age boys become rather sexist. For them, I was the odd one out and they made me feel very much out of place, apart from the fact that they never passed a ball if they could help it!"

The fact that she attended San Andrea School seems to have influenced her decision to take up sport so wholeheartedly, or at least that is what she believes. "The school was very sports-oriented, my teachers always encouraged me to play and I was always playing with all the school teams - we had some very good teams there." Her step into a women's team came about after she was spotted by a scout in an interschool tournament she was playing in. The national team coach and manager of the Hibernians women's team eventually saw her play and she impressed them enough to prompt an invitation to join both Hibernians F.C. and the under-15 women's national football team.

Today Francesca plays both with the Hibs women's football team in first division as well as in the Malta National women's football team. For now Francesca is happy to be still training with the National team, waiting for the stage where she can make it to the best 18. "I find it is hard for me to make it into the National team because of my studies. With regularity, I have to miss training for four weeks at a stretch due to exams. My priorities this year after my medical course semester is finished are to win the league and to get chosen with the first 18 players on the national team."

We steer away from discussing sports and focus on a different topic – Francesca's medical studies at the University of Malta. Interestingly enough, Francesca is the daughter of the late Dr Karl Chircop who was also a member of parliament. She

"I WANT TO BE AS GOOD AS MY FATHER WAS"

immediately mentions him and how his early passing influenced her decision regarding her future profession. "Dad passed away over five years ago and he had always inspired me. Before sixth form I kind of knew I wanted to do medicine, but I never felt like it was really my decision. Then after he died, I realised how much people respected him and his work, and how patients used to look up to him in admiration. It was then that I made my decision and knew medicine was going to be what I would do. I want to help and make people happy like my father did."

The fact that her older brother is now a doctor has also intensified her wish to carry on in this profession. Will she take up something related to sports medicine perhaps? "I want to be as good as my father was. Perhaps I will not become a medical doctor working in family medicine, since I really like surgery as well as psychiatry. But I still have not decided yet." Even whilst she loves the possibility of a hands-on specialisation, and is interested in the way the operating theatre works, she has made the wise decision to cross her bridges only when she comes to them. Nowadays what does help her is time management especially since she is undergoing training in preparation for a possible summer employment. With three more years to go at university and a lively lifestyle to keep up with, Francesca has a lot going on for her. "I'd love to make it into the national women's football team, so that's something I am eyeing. For the rest, I will keep on studying and let things fall in place ... they somehow always do."

QUIZ

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MR MARCO MICALLEF B.PHARM. (HONS.) IS THE LUCKY WINNER. HE WAS THE 5TH PARTICIPANT WHO REPLIED CORRECTLY TO THE QUESTION, 'WHO IS SPONSORING THE VACCINES SECTION OF THE SYNAPSE APP?'. THE CORRECT ANSWER IS PFIZER.

IMAGING INFLAMMATORY BOWEL DISEASE

PIERRE VASSALLO

Inflammatory bowel disease (IBD) refers to a group of idiopathic conditions of the gastrointestinal tract, the most common of which are Crohn's disease and ulcerative colitis (UC). Approximately one in every four to six patients with IBD presents in childhood or adolescence. The incidence of IBD has been increasing over the past 40 years.

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that is characterized by waxing and waning symptoms, transmural inflammation of the bowel wall (i.e. all three bowel wall layers), and skip lesions. It may effect any portion of the gastrointestinal tract, in contrast to UC which only effects the colon . UC lesions are also contiguous and do not penetrated beyond the mucosal layer unlike, Crohn's disease.

IBD can be diagnosed or monitored using a variety of methods, including clinical or hematologic assessment, endoscopy, and imaging. In recent years, an increase in the number of methods used to visualize the bowel has become available, including capsule endoscopy, CT enterography, and MR enterography, with each study having its advantages and disadvantages.

CT or MR enterography is tailored to evaluate the small bowel and its mucosa. Both studies provide exquisite detail of the bowel wall, including its thickness and mucosa, while also allowing detection of the extraenteric manifestations and complications of IBD.

Both CT and MR enterography provide high quality small bowel imaging. CT enterography has the advantages of better spatial resolution, fewer motion artifacts, lower cost, shorter examination times and increased tolerance by claustrophobic patients. On the other hand, MR enterography has the advantage of not using ionizing radiation; this is therefore preferable in children and in pregnant women. MR enterography offers also higher contrast resolution and better evaluation of perianal disease, while also allowing assessment of peristalsis through dynamic imaging.

When comparing CT or MR enterography to traditional small bowel barium follow-through exam, the former are more accurate in detecting IBD, while CT enterography performed on ***new generation scanners*** that use iterative reconstruction technologies, exposes the patient to a smaller radiation dose than a small bowel barium exam.

Small bowel endoscopy rarely covers the whole small bowel and therefore misses a significant number of cases with small bowel inflammatory disease. Capsule endoscopy is performed with an 11 x 27mm capsule that is swallowed by the patient and that records images as it passes through the gastrointestinal tract. It is superior to all other tests for detecting mucosal changes, however it is unable to detect transmural extent of disease and extraenteric manifestations. The capsule is difficult to swallow particularly in children. In addition, due to the frequent presence

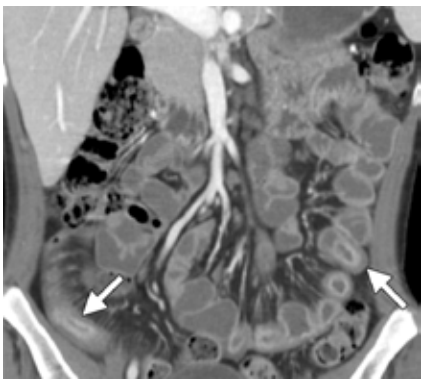

Figure 1. Coronal CT enterographic image showing multiple areas of bowel wall thickening throughout the abdomen (arrows) in this patient with Crohn's disease.

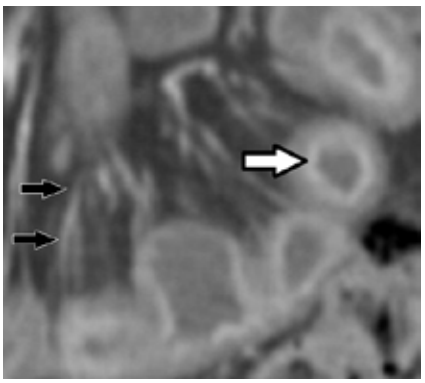

Figure 2. Coronal CT enterographic image showing mucosal enhancement and mural stratification (white arrow) as well as engorged mesenteric blood vessels (vasa recta) (black arrows) in this patient with Crohn's disease.

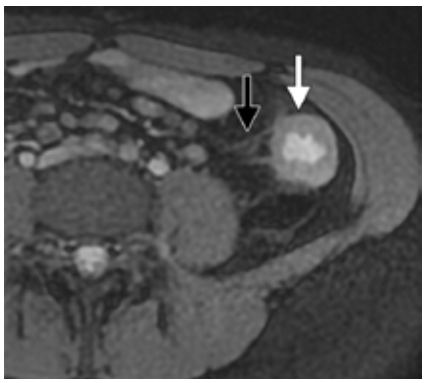

Figure 3. MR enterographic image shows bowel wall thickening of the descending colon (white arrow) and wispy increased signal intensity in the surrounding pericolonic fat (black arrow).

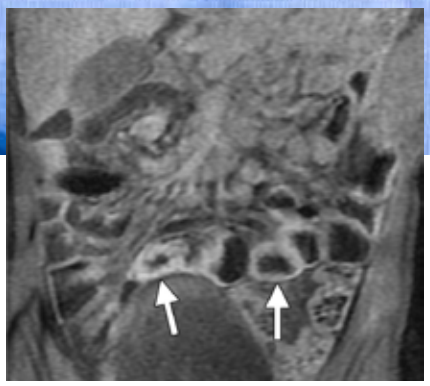

Figure 4. Coronal post-IV contrast T1-weighted MR enterographic image showing discontinuous regions of bowel wall thickening and mucosal enhancement (arrows).

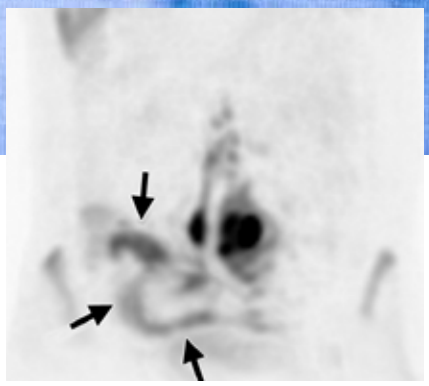

Figure 5. Coronal diffusion-weighted image with background body shows an S-shaped area of restricted diffusion corresponding to the terminal ileum (arrows).

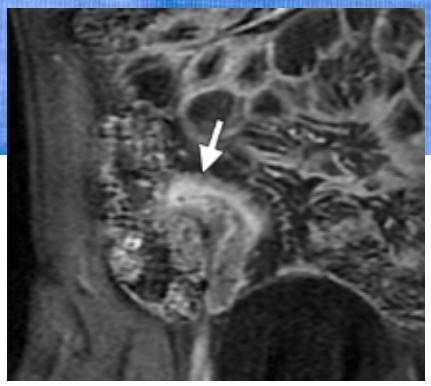

Figure 6. Coronal CT enterographic image showing narrowing of the lumen of the terminal ileum (white arrow) in Crohn's disease.

of bowel strictures particularly in Crohn's disease, there is a high risk of capsule retention (8%), which would consequently require open surgery further increasing the risk of complicating structures, fistulae and abscess formation. Thus a barium study is required prior to capsule endoscopy in order to exclude strictures and minimize the risk of capsule retention.

The technique for performing CT or MR enterography is quite complex and is beyond the scope of this article. The imaging findings are similar on both CT and MR imaging; they can be divided into (1) intestinal and (2) extra-intestinal findings.

1. INTESTINAL FINDINGS

The intestinal findings include bowel wall thickening (bowel wall thickness >3mm in a distended loop), mucosal enhancement, mural layering, skip lesions, luminal narrowing/strictures and fistula. Bowel wall thickening (Fig 1) is the most common finding in IBD particularly in Crohn's disease. Mucosal enhancement is the strongest indicator of acute inflammation and is often accompanied by mural stratification (Fig 2). Bowel wall thickening is also clearly evident on MR enterography (Fig 3) as is mucosal enhancment (Fig 4). Mural stratification may also be the result of fat deposition in between the mucosa and serosa; this occurs in chronic IBD and can be confirmed with fat suppression techniques on MR enterography. Skip lesions are discontinuous areas of inflammation in either the small bowel or colon and are characterized by either mucosal enhancement or bowel wall thickening; these are pathognomonic of Crohn's disease (Fig 4).

Diffusion-weighted imaging (DWI) is a special technique that is available on MR imaging, which measures the diffusivity of extracellular water. Acutely inflammed bowel has an excess

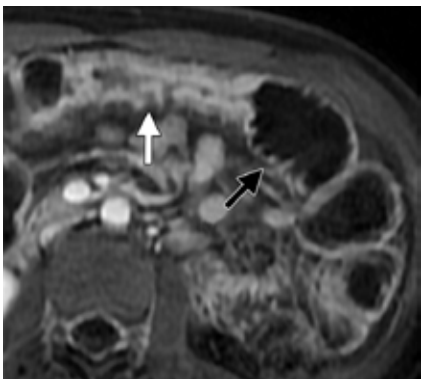

Figure 7. Axial contrast enhanced T1-weighted image shows a strictured segment of small bowel (white arrow) and dilatation of the more proximal small bowel (black arrow).

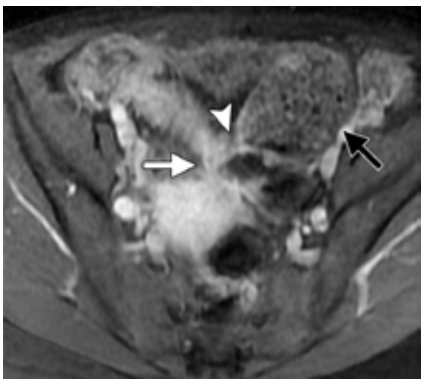

Figure 8. Axial T1-weighted MR entrograph shows a fistula between the colon and uterus (white arrow), a short-segment stricture (arrowhead) just proximal to the fistula and more proximal small bowel dilatation (black arrow).

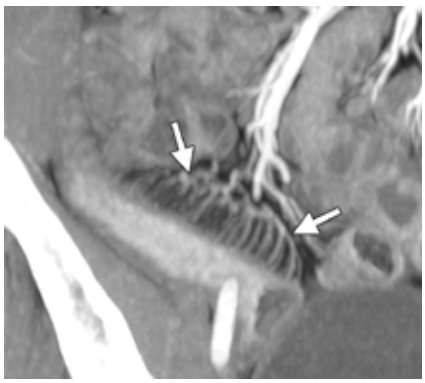

Figure 9. Oblique coronal CT enterographic image shows abnormal bowel wall thickening, mucosal hyperenhancement of the terminal ileum and engorgment of the vasa recta (arrows) creating the comb sign.

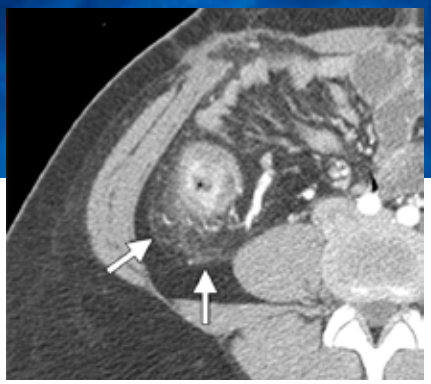

Figure 10. Fat stranding within the pericecal fat (arrows) seen on axial CT enterography.

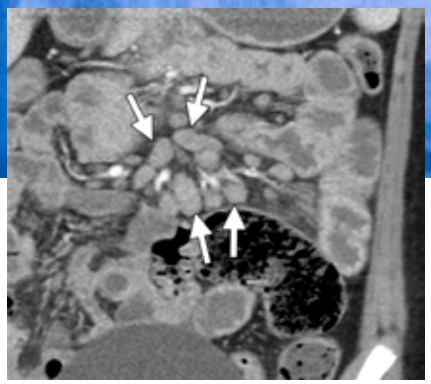

Figure 11. Prominent mesenteric lymph nodes (increase in size and number of lymph nodes) (arrows) seen on coronal CT enterography.

of extracellular fluid that naturally has a high diffusivity; this is well seen on DWI and can be used to identify active bowel wall inflammation (Fig 5).

Luminal narrowing and strictures may be identified either through actual narrowing of the luminal diameter (Fig 6) or indirectly through dilatation of the more proximal bowel loops (Fig 7).

Patients with Crohn's disease have a 20–40% lifetime risk of fistula formation and the most common fistulas are enterocutaneous, enteroenteric, and perianal fistulas (Fig 8).

2. EXTRA-INTESTINAL FINDINGS

The extra-intestinal findings include engorgement of mesenteric vessels (comb sign), mesenteric infiltration, increased mesenteric fat, lymphadenpathy, fluid collections (abscess formation) and ascites. Engorgement of the vasa recta is a finding of active inflammation in IBD and is caused by increased blood flow through the vasa recta to inflamed segments of bowel; this may result in the comb sign (Fig 9). Extension of inflammation outside the bowel wall results in mesenteric infiltration that appears as fat stranding on MR and CT enterography (Fig 10). An increase in number and size of mesenteric lymph nodes (frequently only mildly enlarged) is seen in IBD (Fig 11).

Other non-bowel related features, which include gall stones, nephrolithiasis, primary sclerosing cholangiitis, sacroiliitis and thromboembolism are all detected on images obtained during CT and MR enterography.

CT and MR enterography are safe and effective methods for diagnosing and evaluating IBD; unlike previous x-ray contrast techniques and endoscopy, these methods allow radiologists to interpret intestinal and extra-intestinal findings that are widespread and which are of great importance in these patients.

ANNOUNCEMENT

NEW POSTGRADUATE DOCTORATE OF PHARMACY PROGRAMME IN EUROPE

The University of Malta in collaboration with the University of Illinois in Chicago is launching a new postgraduate Doctorate of Pharmacy programme, PharmD. The course starts in October 2014 and is intended to attract pharmacists who would like to develop their clinical pharmacy and research skills to a doctorate degree while empowering pharmacists to assume leadership roles that will drive policies and developments in clinical practice and service that draws on scientific, evidence-based and innovative research. The Pharm D course is spread over three years of study (6 semesters). The first year of study is mainly composed of taught units with the second and third years being based primarily on research and clinical experience. The taught programme covers aspects of Pharmacotherapeutics, Drug information and statistics, Pharmacoeconomics and Health systems in Europe and the USA. The **Clinical Experience** will be provided through clinical rotations based in different pharmacy settings including hospital, ambulatory care and community pharmacy. The **Research** modules will lead the candidate to develop critical analysis and literature evaluation within the context of translational and applied research in pharmacy. All study-units are delivered jointly by the two universities through lectures, distance learning and practice-based learning. This course presents a unique opportunity for pharmacists in all areas to acquire a doctorate degree reflecting present and future international developments in pharmacy.

Funding: A number of paid traineeships for a 28 hour per week with a stipend of 1000 euro per month are available in the following pharmaceutical areas: hospital, community, procurement, informatics, distribution, regulatory and industrial. For further information contact Prof. Lilian M. Azzopardi of the Department of Pharmacy at the UOM on lilian.m.azzopardi@um.edu.mt or Prof. Alan Lau from the College of Pharmacy University of Illinois on alanlau@uic.edu. Website: http://www.um.edu.mt/imp/courses/doctor-of-pharmacy.

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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: Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. *Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 6x1 or 30x1 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/001 - EU/1/13/862/003 **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 22983217/+35621222872 2014-MT-ULT-28-MAY-2014

References: 1. Novartis Europharm Ltd. Ultibro® Breezhaler® Summary of Product Characteristics. 2. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1:51-60. 3. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013; 42(6): 1484-1494 doi: 10.1183/09031936.00200212. Epub 2013 May 30. 4. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209.

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NOVARTIS PHARMACEUTICALS

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Teveten 600mg Film-coated Tablets: Pharmaceutical Form: Film-coated tablets containing eprosartan mesylate equivalent to 600mg eprosartan free base. **Indication:** Essential hypertension. **Dosage and Administration:** Adults: 600mg once daily taken in the morning with food. .Maximal blood pressure reduction may take 2-3 weeks. Teveten may be used alone or in combination with other anti-hypertensive medication. No dose adjustment is required in the elderly. Teveten is not recommended in children and adolescents due to lack of safety and efficacy data. No dose adjustment is required in hepatic impairment. In patients with moderate or severe renal impairment (CCL<60ml/min), the daily dose should not exceed 600mg. **Contraindications: Hypersensitivity** to components, pregnancy (second and third trimesters), lactation, haemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney. Special **Warnings and Precautions for use:** Caution in patients whose renal function is dependent on the renin-angiotensin-aldosterone system. In patients with renal impairment, assess renal function before starting and at intervals during therapy. Caution in patients with CCL <30ml/min or in those undergoing dialysis. At the start of therapy symptomatic hypotension may occur in patients with severe sodium and/or volume depletion, correct before commencing therapy. There is an increased risk of severe hypotension in patients with bilateral renal artery stenosis or stenosis of the artery to a single kidney. Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy. Monitor serum potassium levels in renally impaired patients when drugs that may increase potassium are administered with Teveten. Not recommended in primary hyperaldosteronism. **Drug Interactions:** Attenuation of antihypertensive effect and risk of worsening renal function may occur with concomitant administration of NSAIDs, COX-2 inhibitors or aspirin (>3g/day). Monitor serum lithium levels during concomitant use. **Pregnancy and Lactation:** Not recommended during the first trimester of pregnancy. Teveten should not be used during the second and third trimesters of pregnancy. Not recommended during breast- feeding. **Effect on the ability to drive and operate machinery:** Based on its pharmacodynamic properties, eprosartan is unlikely to affect the ability to drive or use machines. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension. **Undesirable Effects:** *Very Common:* Headache; Common: Dizziness, rhinitis, allergic skin reactions, arthralgia, asthenia, flatulence and unspecific gastrointestinal complaints. Uncommon: Hypersensitivity, hypotension and angioedema. **Name and Address of Marketing Authorisation Holder:** Abbott Healthcare Products Limited. **Marketing Authorisation Number:** 1009/00601.

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