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# THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- Role of Gastrointestinal Bacteria in Obesity and Type 2 Diabetes
- Negligence and Civil Liability in the Medical Profession
- German-Maltese Medical Society Update
- Toxicology in the Movies

Volume 15, 2016 Issue 01

ISSN number 2313-8084


## 1981. Augmentin® – The first clavulanate-potentiated amoxicillin was launched for oral use[2]

# LEADERS WALK IN FRONT


1. Available at http://www.history.com/this-day-in-history/columbus-sets-sail accessed on 28 May 2014
2. White AR *et al.* Augmentin™ (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent; Journal of Antimicrobial Chemotherapy 2004; 53: S1 i3-i20


**Abridged Prescribing Information:** *Please refer to full Summary of Product Characteristics before prescribing.* **Trade name:** Augmentin 500 mg/125 mg film coated tablets; Augmentin 875 mg/125 mg film-coated tablets; Augmentin SR 1000 mg/62.5 mg prolonged-release tablets. **Active Ingredient:** Amoxicillin trihydrate. **Augmentin 500 mg/125 mg:** Each tablet contains 500 mg amoxicillin and 125 mg clavulanic acid; **Augmentin 875 mg/125 mg:** Each tablet contains 875 mg amoxicillin and 125 mg clavulanic acid; **Augmentin SR 1000 mg/62.5 mg prolonged-release tablets:** Each tablet contains 1000 mg amoxicillin and 62.5 mg clavulanic acid. **Pharmaceutical form: Augmentin 500 mg/125 mg & 875/125 mg:** Film coated tablets; **Augmentin SR 1000 mg/62.5 mg:** Prolonged release tablets. **Indications: Augmentin 500 mg/125 mg & 875/125 mg:** Acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia, cystitis, pyelonephritis, skin and soft tissue infections, animal bites, severe dental abscess with spreading cellulitis, bone and joint infections; **Augmentin SR 1000/62.5 mg tablets:** are indicated for the treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **Posology and Method of Administration:** Oral use. **Augmentin 500 mg/125 mg:** Adults and children ≥40 kg: One tablet three times a day. Children <25 kg: Children must not be treated with Augmentin tablets. **Augmentin 875 mg/125 mg:** Adults and children ≥40 kg: standard dose (for all indications) 875 mg/125 mg two times a day; higher dose (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day. Children <40 kg: Children may be treated with Augmentin tablets, suspensions or paediatric sachets. **Augmentin SR 1000/62.5 mg:** Adults and adolescents ≥16yrs: Recommended dose of two tablets twice daily for seven to ten days. Caution in patients with hepatic impairment and monitor hepatic function at regular intervals. In patients with renal impairment dose adjustments are based on the maximum recommended level of amoxicillin. To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption is optimised when taken at the start of a meal. *Refer to SPCs for further administration and dosage guidance.* Children <16yrs: Not indicated. For all strength/formulations, treatment should not be extended beyond 14 days without review. **Contraindications:** Hypersensitivity to the active substances, to any penicillins or to any of the excipients; patients with history of hypersensitivity to beta-lactam antbiotics; history of amoxicillin/clavulanic acid associated jaundice/hepatic impairment. **Special Warnings and Precautions:** Before initiating therapy careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta lactams. Serious and occasionally fatal hypersensitivity reactions have been reported. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. *Refer to SPCs for full list.* **Interactions with other medicaments:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **Fertility, Pregnancy and Lactation:** Use should be avoided in pregnancy unless considered essential by the physician. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician. **Effect on Ability to Drive or Use Machines:** No studies, however undesirable effects such as dizziness may occur. **Side Effects:** Very common (≥1/10): diarrhoea; Common (≥1/100 to <1/10): mucocutaneous candidosis, nausea, vomiting. *Refer to SPCs for full list of undesirable effects.* **Overdose:** Gastrointestinal symptoms may be treated symptomatically. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis. **Local Presentations: Augmentin 500 mg/125 mg**: 21 tablet packs; **Augmentin 875 mg/125 mg**: 14 tablet packs; **Augmentin SR 1000/62.5 mg:** 28 tablet packs. **Marketing Authorisation Holders: Augmentin 500 mg/125 mg & 875 mg/125 mg**: GlaxoSmithKline (Ireland) Ltd; **Augmentin SR 1000/62.5 mg:** GlaxoSmithKline Bulgaria EOOD. **MA Numbers: Augmentin 500 mg/125 mg:** MA 192/01503; **Augmentin 875 mg/125 mg:** MA 192/01502; **Augmentin SR 1000/62.5 mg:** AA 1051/00102. **Legal category:** POM. **Date of revision of text:** December 2015.

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

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

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

Job No: MLT_GIB/CAM/0009/15 Date of Preparation: December 2015

# DOCTORS AS INTELLECTUALS

GUEST EDITORIAL

**PROF. MAURICE CAUCHI** MD MSc PhD DPH
FORMER DIRECTOR OF PATHOLOGY, MINISTRY OF HEALTH, MALTA

The medical profession is arguably the most respected profession, and has been so for centuries. It is seen by the general public as one which can be trusted with the most intimate problems, individual or family, medical or social.

It has also been the case that, particularly in the past, doctors have spread their wings beyond the limits of medical practice and have been involved in politics, literature and various aspects of Maltese culture.

It is true that medical practitioners are considered to be very busy with work within their speciality and have little time or inclination to widen their interests to reach out to the general public. One might also expect that any intellectual input should come primarily from the academic members rather from those involved in the day-to-day work at the coalface.

There is, however, a great need for medical practitioners to become more visible within the framework of society, not just as dispensers of medical advice and medication, but also to become involved in issues of public concern.

One issue of concern is the obvious lack of medical (or even basic biological knowledge) within the community. Science in general, but particularly medical science seems to be at a nadir, neglected to a large extent in schools, and evident not only in the illiterate but even in many of those practicing other professions. In this respect it is encouraging to see medical students writing about medical matters in the local papers. This is certainly an area where most medical practitioners can be involved, whether in print, radio, television, or the more recently introduced social media which seem to include everybody these days.

Perhaps more worrying are the current changing mores relating to ethical issues. Time was when most of us got our ethical substratum from teaching by the church which used to be so predominant in influencing ethical thinking within society. These days, for better or worse, the influence of the church has diminished very considerably, particularly among the younger members of society, leaving a gaping void.

Everyone seems entitled to express their considered but untutored views on any topic. I believe that the medical profession should be at the forefront in informing the public about ethical issues relating to the many aspects of medical and social problems.

Perhaps related to this is the lack of familiarity with basic issues inherent in an education in the humanities, with its emphasis on elucidation of basic ethical and social issues within the community.

Maybe members of the medical profession may feel diffident in discussing issues which are not strictly and narrowly medical. While medical education is the most essential requisite, it should serve as a springboard to launch into wider societal issues. Who else, professional social workers apart, would be more familiar with the widespread issues which many practitioners face every day, issues such as the effects of poverty, domestic violence, child abuse, old age, single motherhood, reproductive technology, and a raft of other societal issues?

Various definitions of 'intellectual' have been proposed. A trivial dictionary definition, 'a person possessing a highly developed intellect' is obvious enough but this is just a minimum requirement. It is more important to emphasize the role of such individuals in spreading their knowledge and expertise to the general community, and not merely within the coterie of colleagues and related experts.

We can all be intellectuals if we use our special knowledge to engage with the public to tackle a wide range of educational and social issues. As that wise philosopher/statesman Edmund Burke remarked: *"All that is needed for the forces of evil to succeed is for enough good men to remain silent."*

Cover: **Klingon Bird-of-Prey attack squadron by Prof. Victor Grech**. In *Star Trek*, the Klingon Bird-of-Prey was a small warship used by the Klingon Empire from the late 22nd century to the 24th century

Oil on canvas with painting knife

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*A maintenance bronchodilator treatment for patients with COPD who are breathless*


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

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

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

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

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

Theravance

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

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## ISSUE GUIDE



TheSynapse

# The Powerful Amoxicillin + Clavulanic Acid Combination

## Forcid Solutab®:

- Contains amoxicillin and clavulanic acid in the ratio 7:1, the powerful combination to fight infections in unique Solutab® formulation

## Forcid Solutab® indications:

- Acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia.
- Cystitis, pyelonephritis.
- Skin and soft tissue infections in particular cellulitis, animal bites.
- Severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

## Forcid Solutab® offers a convenient antibiotic therapy for adults and children:

- Easy and flexible administration, the unique versatile formulation can be swallowed intact or dissolved in water.
- Equally effective whether dissolved in water or taken as a tablet and rapidly absorbed.[1]
- Suitable for a wide range of patients: no sugar, no gluten, no sodium, no lactose.

## Forcid Solutab® dosing in adults and children ≥ 40 kg:

- Standard dose of Forcid Solutab 1000 is 2 times a day.
- For infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections, Forcid Solutab1000 is recommended to be given 3 times per day.

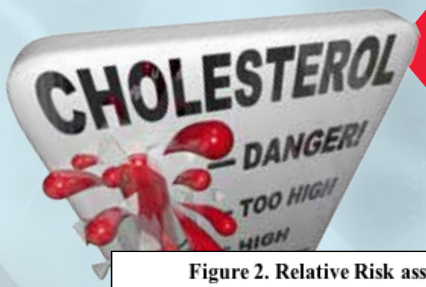
**Forcid® 1000 Abbreviated Prescribing Information. Presentation:** Forcid® 1000, containing as active substances amoxicillin and clavulanic acid. Each tablet/dispersible tablet contains 875 mg amoxicillin as amoxicillin trihydrate and 125 mg clavulanic acid as potassium clavulanate. **Indications:** Amoxicillin/clavulanic acid tablets are indicated for the treatment of the following infections in adults and children: acute bacterial sinusitis (adequately diagnosed), acute otitis media, acute exacerbations of chronic bronchitis (adequately diagnosed), community acquired pneumonia, cystitis, pyelonephritis, skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis, bone and joint infections, in particular osteomyelitis. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Duration of therapy:** The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review. **Posology:** The dose of amoxicillin/clavulanic acid that is selected to treat an individual infection should take into account the expected pathogens and their likely susceptibility to antibacterial agents, the severity and site of infection, the age, weight and renal function of the patient. **Adults and children over 40 kg:** The standard dose of Forcid 1000 is 2 times a day. For infections such as otitis media, sinusitis, lower respiratory infections and urinary tract infections, Forcid 1000 is recommended to be given 3 times per day. **Children under 40 kg:** 25mg/3.6mg/kg/day to 45mg/6.4mg/kg/day given as 2 divided doses. No clinical data are available for amoxicillin/clavulanic acid 7:1 formulations higher than 45mg/6.4mg/kg per day in children under 2 years. There are no clinical data for amoxicillin/clavulanic acid 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population cannot be made. **Elderly patients:** No dose adjustment is necessary. **Patients with impaired renal function:** No dose adjustment in dose required in patients with creatinine clearance (CrCl) greater than 30ml/min. In patients with CrCl less than 30ml/min, use of Forcid 1000 is not recommended as no recommendations for dose adjustments are available. **Patients with impaired liver function:** Dose with caution and monitor hepatic function at regular intervals. **Method of administration:** Amoxicillin/clavulanic acid tablets are for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption. Forcid tablets can be swallowed whole with a glass of water, or first dissolved in a ½ cup of water (at least 30ml) and stirred thoroughly before swallowing. **Contraindications:** Hypersensitivity to the active substances, to any penicillins or to any of the excipients. History of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **Special warnings and precautions for use:** Before initiating therapy, careful enquiry should be made of previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in patients with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid must be discontinued and appropriate alternative therapy instituted. If an infection is proven to be due to amoxicillin-susceptible organism(s), consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance. This presentation of amoxicillin/clavulanic acid is not suitable for use when there is high risk that presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should also not be used to treat penicillin-resistant *S. pneumonia*. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Avoid if infectious mononucleosis is suspected. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. Prolonged use may result in overgrowth of non-susceptible organisms. Occurrence of feverish generalised erythema associated with pustula at treatment initiation may be a symptom of acute generalised exanthemous pustulosis (AGEP) and requires treatment discontinuation and contra-indicates any subsequent administration of amoxicillin. Use with caution in patients with evidence of hepatic impairment. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects. Antibiotic-associated colitis has been reported, consider in patients who present with diarrhoea. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation. Periodic assessment of organ system functions is advisable during prolonged therapy. Prolongation of prothrombin time was reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. In patients with renal impairment, dose should be adjusted according to degree of impairment. In patients with reduced urine output, crystalluria has been observed very rarely, mainly with parenteral therapy. Maintain adequate fluid intake and urinary output during administration of high doses of amoxicillin to reduce possibility of amoxicillin crystalluria. If bladder catheter is in-situ, check patency. False positive results may occur when testing presence of glucose in urine with non-enzymatic methods during treatment of amoxicillin; use enzymatic glucose oxidase methods. Clavulanic acid in Forcid may cause non-specific binding of IgG and albumin by red cell membranes leading to false positive Coombs test. Reports of positive test results using Bio-Rad Laboratories Platelia *Aspergillus* EIA test; cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported; positive results should be interpreted cautiously and confirmed by other diagnostic methods. Forcid 1000 contains 0.64 mmol potassium per tablet (25 mg). **Pregnancy and lactation:** Use in pregnancy should be avoided unless considered essential by physician. Both amoxicillin and clavulanic acid are excreted in breast milk; consequently diarrhoea and fungus infection of mucous membranes is possible in breast-fed infants. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by physician in charge. **Undesirable effects:** The most commonly reported adverse reactions (ADRs) are diarrhoea, nausea and vomiting. For a full listing of undesirable effects, refer to the complete Summary of Product Characteristics for Forcid 1000. Marketing authorization holder: Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. 13-FOR-003 Adverse events should be reported to the local regulatory authority and Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. Please read carefully the instructions on the package leaflet. 13-FOR-004 102013

**Reference: 1.** H. Sourgens et al. International Journalof Clinical Pharmacology and Therapeutics. 2004; 42: 165-173.

astellas
Leading Light for Life

Amoxicillin clavulanic acid
FORCID Solutab®

# THE CHOLESTEROL CONTROVERSY - THE SERIES




ALBERT CILIA-VINCENTI

Atherosclerosis remains the number one cause of morbidity and mortality in most countries. After almost a century of research, the creation of a huge industry in blood cholesterol testing and marketing of statins, as well as significant advances in interventional cardiology and coronary by-pass surgery, the causation and pathogenesis of atherosclerosis remains, as yet, not only poorly understood, but actually controversial.

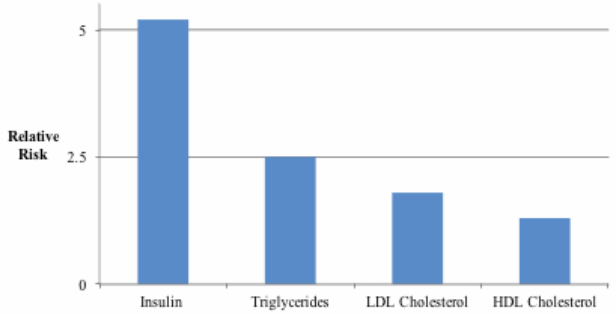
If the risk factors for atherosclerosis remain poorly understood, and some very controversial, it is no wonder that in spite of improved survival from coronary heart disease (CHD) (due to all the efforts and funds spent on investigations and treatment), there is no good evidence that the incidence of atherosclerosis has significantly decreased.

Many doctors leave medical school with a poor knowledge of physiology and biochemistry and come to rely blindly on information imparted from pharmaceutical companies, the latter also influencing clinical research with their funding. So let's go back to some basic science and clinical research from as far back as the 1960s which, although apparently largely forgotten, remains valid.

Blood insulin (hyperinsulinaemia and insulin resistance) has been claimed to be the most important predictor of CHD.[1-12] However, this has been largely ignored because the "dietary saturated fat, blood cholesterol and CHD" theory has prevailed and spawned the multi-billion statin industry, directed at lowering LDL-cholesterol. But around 50% of patients hospitalised with CHD are reported to have total and LDL-cholesterol levels within normal limits.[13]

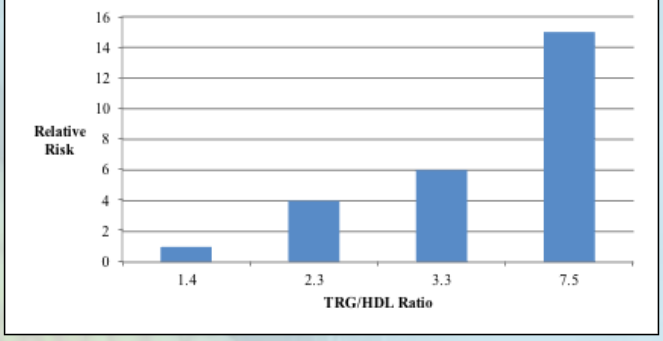
A study which looked at fasting blood insulin levels compared with conventional risk factors, to see which was more predictive of developing CHD over a 5-year period in clinically disease-free individuals, found that fasting insulin levels were more than twice as predictive compared to LDL-cholesterol (Figure 1).[14] Triglycerides (TRG) were also more predictive than LDL.[15-16] In fact, one of the first signs of hyperinsulinaemia is increased TRG. Although HDL by itself is a less powerful predictor than LDL, when the increase in risk of elevated TRG is multiplied by the increase in risk of decreased HDL, the result is very close to fasting insulin as risk predictor for CHD. The fasting TRG/HDL ratio is in fact a surrogate marker for fasting insulin.[17-20]

**Figure 1. Relative Risk association with Risk Factors for Atherosclerosis**




*Source: Lamarche B, Tchernof A, Mauriège P, Cantin B, Dagenais GR, Lupien PJ et al. Fasting insulin and apolipoprotein B levels and low-density particle size as risk factors for ischaemic heart disease. JAMA 1998:279; 1955-1961*

**Figure 2. Relative Risk association with TRG/HDL Ratio**




*Source: Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ et al. Small, dense LDL particles and the risk of ischemic heart disease: Prospective results from the Quebec Cardiovascular Study. Circulation 1997:95; 69-75*

You will remember from previous instalments that what routine laboratories measure as LDL consists of two fractions, one large and light and the other small and dense. The latter is very prone to oxidation and claimed to be related to atherosclerosis.[21] The other fraction is reckoned not be related to CHD. In routine laboratory estimates of LDL levels one does not know which LDL fraction predominates. However, high fasting TRG/HDL ratios have been associated with high levels of the small dense LDL fraction, and the TRG/HDL ratio is therefore a convenient surrogate marker for the small dense LDL fraction.[22]

A study comparing patients who had survived their first heart attack with matched patients without a history of CHD, found (Figure 2) that those with the highest TRG/HDL ratios were 16 times more likely to have a heart attack than those with lower ratios.[23] This is a dramatic finding. Do you know which drug lowers the TRG/HDL ratio? No, it's not statins. It's a low-carbohydrate with adequate protein and saturated and monounsaturated fat diet.[24,25]

The conventional wisdom driving the "dietary saturated fat, blood cholesterol and CHD" band-wagon continues to advise doctors and the general public to reduce dietary fat at all costs. But dietary fat has no direct effect on blood insulin. Even way back in 1997, leading nutritional researchers wrote in the New England Journal of Medicine that there is no persuasive data supporting the hypothesis that a low-fat, high-carbohydrate diet has any long-term benefit in treating obesity, CHD and cancer.[26] Why? Because each of these diseases is associated with hyperinsulinaemia. Fat has no effect on insulin secretion, whereas carbohydrates have a major stimulatory effect.

In conclusion, it is most unfortunate that the US governmental nutritional advice continues to recommend severe restriction of dietary saturated fat. Also worrying are, (a) the continuing conventional wisdom that LDL is the prime indicator of CHD risk, (b) the lack of recognition that the TRG/HDL ratio is the most predictive of all the routine blood lipid profiles, and (c) that statin therapy protocols based mainly on routine LDL levels (without knowledge of LDL dense sub-fractions) are of suspect validity. Statins might be a blunderbuss therapy whose positive effect on established CHD may be only via their anti-inflammatory action, similar to the far cheaper aspirin.

Whether adding more expensive predictive tests, such as high-sensitivity C-reactive protein (HsCRP) and the PLACtest®, improves mortality from CHD (compared to the routine TRG/HDL ratio), is not yet clearly established.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

The First Once-Daily Dual Bronchodilator[1]

# THE FIRST ONCE-DAILY DUAL BRONCHODILATOR
# ULTIBRO® BREEZHALER®

## Once-daily ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).[1]

**Ultibro Breezhaler inhalation powder, hard capsules**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **PRESENTATION:** Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. Method of administration For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. Asthma: Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium: Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. Urinary retention: No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/033 , EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc. Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872 2015-MT-ULT-09-OCT-2015

1. Novartis Europharm Ltd. Ultibro Breezhaler Summary of Product Characteristics.


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

NOVARTIS
PHARMACEUTICALS

ULT Ad1 01/16 MT

SONIA VANCELL
FRANCO VASSALLO

# NEGLIGENCE AND CIVIL LIABILITY IN THE MEDICAL PROFESSION - PART II

> ...THE 'BOLAM TEST' [IS] THE BEST KNOWN AND OFTEN QUOTED DEFINITION OF STANDARD OF CARE REQUIRED FROM DOCTORS

As referred to in the first part of this article, for an aggrieved party to succeed in his claim he must prove to the satisfaction of the court the three elements of negligence, that is:

i. the physician had a duty of care in that particular situation,
ii. the physician failed to discharge the standard of care required by that duty, and
iii. he has suffered damages in consequence of a breach of that duty.

Reference to the first element, that is, that the medical professional has a duty to provide the patient with care in accordance with an accepted standard, has already been made in the first part of this article.

***C.ii.b Breach of Duty***

Once the duty of care has been demonstrated, a claimant must then prove that the doctor failed to meet this duty; in other words, that the care provided (or lack of it) has fallen below the minimum acceptable standard. An area that has been extensively debated in the courts is how this standard is to be quantified. Although this is a topic of ongoing debate, the basic test remains the 'Bolam test', the best known and often quoted definition of standard of care required from doctors. In the English case 'Bolam vs Friern Hospital Management Committee'[1] which was decided by Mr Justice McNair, the applicant contended that the doctor was negligent in the manner the therapy was administered and it was alleged that as a consequence he had a lot of complications. The patient brought an action against the doctor in negligence. The judge declared that a doctor is not guilty of negligence *"if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art."* In other words a doctor is not negligent if his actions are supported by a responsible body of medical opinion; the judgement meant that the act of the doctor had to be examined in the light of the practice followed by a responsible body of medical opinion practicing in a similar field of medicine. In this case, Mr Justice McNair delivered a verdict in favour of the defendant hospital.

To determine whether there has been negligence in medical treatment, courts usually follow the same line of enquiry as they pursue in any other claim based on negligence. Courts usually analyse whether the conduct of the defendant amount to a breach of duty of care which he owed to the injured party. As has been stated above, the 'Bolam test' is the standard of the ordinary skilled man professing to have that skill.

There are many cases both in Common Law and Civil Law jurisdictions in which actions for medical negligence have been dismissed on the basis that the doctor conformed to an accepted practice of the profession. It is extremely rare for a commonly accepted practice to be condemend as negligence.

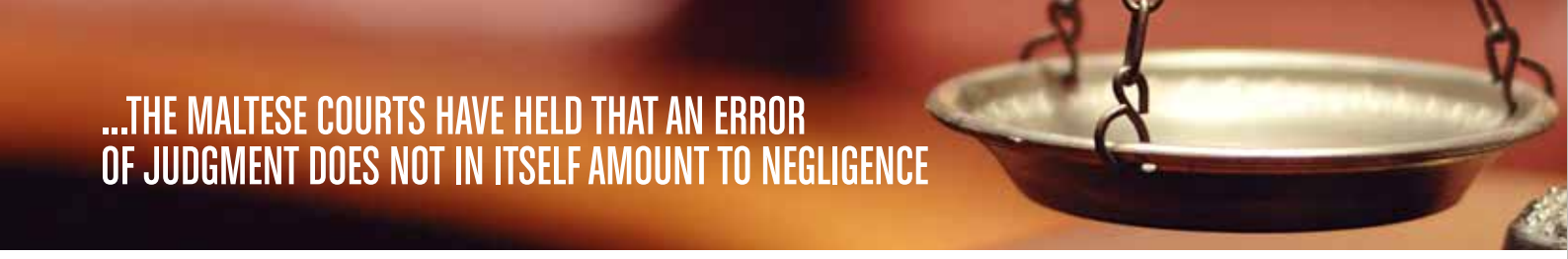
It goes without saying that medicine is not static and is continually evolving. A doctor is expected to keep abreast with the new practices and new treatments and departing from an accepted practice does not, in itself, constitute negligence. Thus, if a doctor can justify why he departed from accepted practice, his actions will not be held to be negligent. The rationale behind this is that the medical profession should not be discouraged from trying new techniques and that there should be the least possible interference with the development of medical science.

***C.ii.c Error in Judgment***

It is pertinent to note that the Maltese courts have held that an error of judgment does not in itself amount to negligence. In the Asphar case[2] the court held that the medical professional cannot be found liable for an error of judgment as long as the error was not the result of negligence or lack of prudence, diligence, and attention of a bonus paterfamilias.

*"Il-Professjonista ma hux tenut għad-danni riżultanti minn żball professjonali, ammenokke' dan l-iżball ma jkunx grossolan, u ammenokke' l-ħtija ma tkunx tista' tigi attributa lilu minħabba nuqqas ta' prudenza, diliġenza u attenzjoni ta' bonus paterfamilias."*

When faced with such a claim, Courts still looked at whether the action taken by the medical professional was in accordance with standard accepted practices.



...THE MALTESE COURTS HAVE HELD THAT AN ERROR OF JUDGMENT DOES NOT IN ITSELF AMOUNT TO NEGLIGENCE

## C.III LINK OF CAUSALITY

For a person to be held liable for negligence the aggrieved party must also establish a link of cause and effect, that is, that he suffered damage and that damage was a result of the doctor's negligence. Our courts have continuously upheld this necessity and in the Ellul case[3] the Court of Appeal held that:

*"Illi hu elementari li 'per dare luogo a responsabilita' e necessario che esista un rapport di causa ed effetto tra il fatto illecito ed il danno".*

The burden of proof lies on the claimant, that is, the person alleging the lack of responsibility of the medical professional.

## D. DAMAGES

## D.I CRITERIA FOR THE IMPOSITION OF RESPONSIBILITY - 'CULPA' AND 'DOLO'

*Culpa* has been defined as 'consisting in the omission of due diligence on account of which one is not aware that one's act is contrary to a provision of the law or that one's omission constitutes the breach of a duty imposed by law.'[4] More often than not, *culpa* arises out of lack of foresight of the harmful consequences of one's act, consequences which would be readily foreseeable by the reasonable man.

When a person acts with a high degree of negligence and/or imprudence then such a high degree of *culpa* approximates to *dolus*. *Dolus* consists in the knowledge that one's act is contrary to a provision of the law or that one's omission constitutes the breach of a duty imposed by law, and that such an act or omission will cause damage.

## D.II AWARD OF DAMAGES

An award of damages is the normal remedy sought by the patient for a breach of duty by a medical practitioner whether the claim is brought in contract or in tort. The central purpose of claims for medical malpractice is to compensate the patient, or his heirs for any loss.

### *D.ii.a Tortious Responsibility*

The Civil Code establishes that the quantum of damages recoverable as a result of tortious responsibility

*'shall be assessed by the court having regard to the circumstances of the case, and particularly, to the nature and degree of incapacity caused, and to the condition of the injured party.'*

Under tort, the damages recoverable, consist in *'the actual loss which the act shall have directly caused to the injured party, in the expenses which the latter may have been compelled to incur in consequence of the damage, in the loss of actual wages or other earnings'*.

These are commonly referred to as the *'damnum emergens'* which are the actual expenses incurred directly as a result of the injury sustained.

The Civil Code also provides for damages recoverable as a result from *'the loss of future earnings arising from any permanent incapacity, total or partial, which the act may have caused'*. These damages are commonly referred to as the *'lucrum cessans'*.

Both *damnum emergens* and *lucrum cessans* can be recoverable irrespective of whether the damage was caused through *culpa* or *dolus*.

### *D.ii.b Contractual Responsibility*

In a breach of contract, there is a difference between the damages recoverable when the obligation is breached due to negligence and the damages recoverable when the breach is due to fraud. In the former case the damages are limited to such damages which 'as were or could have been foreseen at the time of the agreement'. This limitation is non-existent when the breach is due to fraud.

## CONCLUSION

This article has focused on important principles in the field of negligence and a very important conclusion of this study is that as a general rule, a doctor who acts in accordance with the general or commonly accepted practice of other professionals in similar circumstances will not be held to have been negligent. A doctor is under a duty to use that degree of care and skill which is expected of a reasonably competent practitioner in the same class which he belongs, acting in the same and similar circumstances.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1. Bolam v Friern Hospital Management Committee (1957) 2 All ER 118; (1957) 1 WLR 582 pg 586-588.
2. Collection of civil cases. Vol XXXV Pt I pg 55. University of Malta.
3. Collection of civil cases. Vol XLI Pt I pg 80. University of Malta.
4. Professor Victor Caruana Galizia Law notes. University of Malta.

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

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

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

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

# Help Poppy by prescribing Seretide

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

## Safety Information

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

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

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

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


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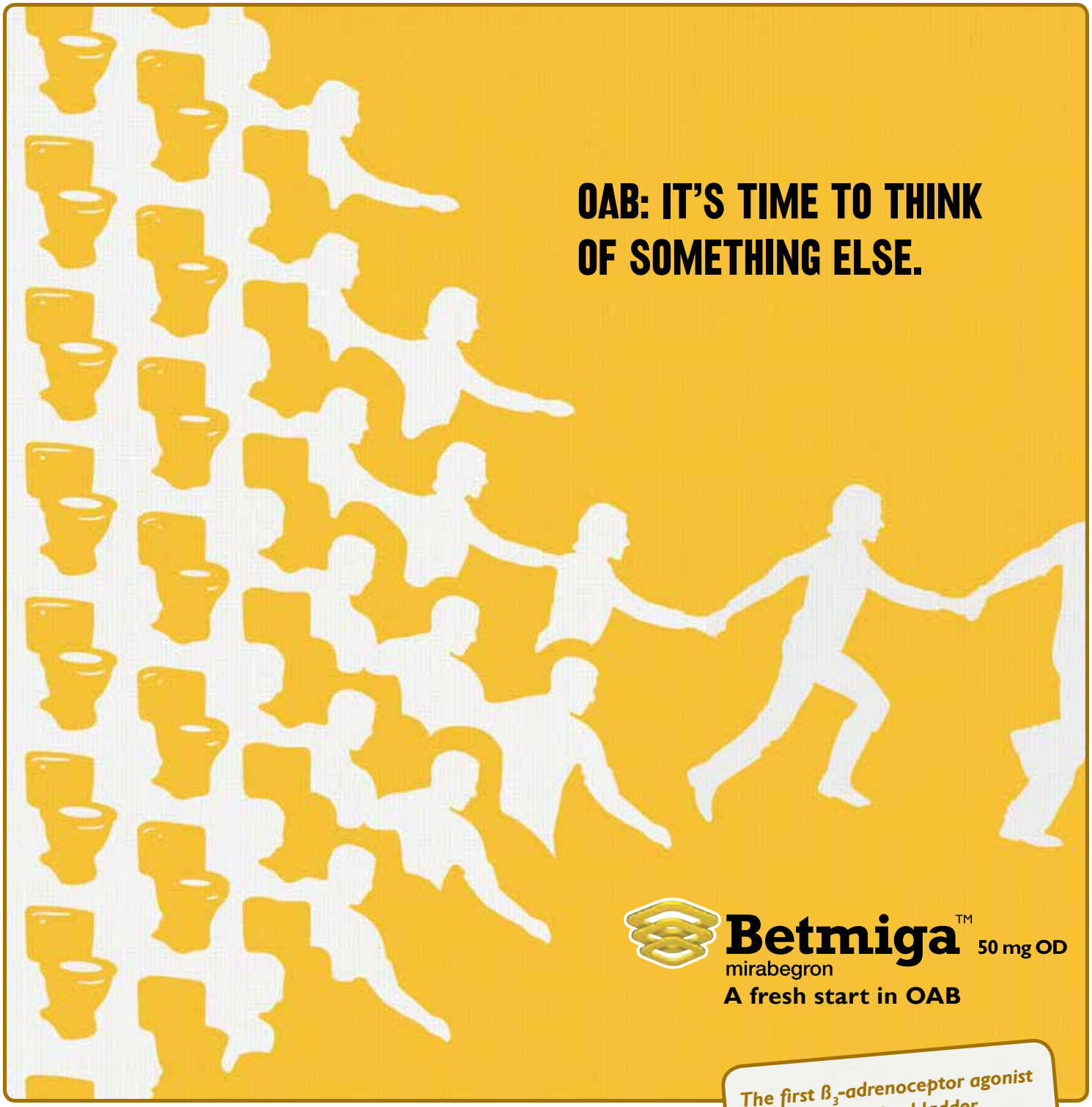
1. Wildhaber, J *et al. Pediatr. Pulmonol* 2012; 47:346–357.
2. DeBlic J *et al. Pediatr Allergy Immunol* 2009: 20:763–771
3. Seretide Evohaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.
4. Seretide Accuhaler (fluticasone propionate/salmeterol xinafoate) Summary of Product Characteristics, Allen & Hanburys Ltd. October 2014.



Date of Preparation: **January 2015** ZINC CODE: **MLT_GIB/SFC/0002/15**


SERETIDE®
salmeterol/fluticasone propionate




astellas

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

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

NIKOLAI PACE

# GASTROINTESTINAL BACTERIA IN OBESITY AND TYPE 2 DIABETES – A REVIEW OF CURRENT KNOWLEDGE

The gastrointestinal tract is home to over $10^{14}$ bacteria that collectively form the intestinal microbiome, and their joint genetic repertoire is larger than the human genome.[1] These symbiotic bacteria establish and maintain the gut immune system, and contribute to the breakdown of complex non-digestible plant-derived polysaccharides.[2,3] The relatively recent technological advances in genomics have revolutionized the study of the intestinal microbiome. It is now possible to sequence mixed microbial genetic material directly extracted from environmental samples without prior laboratory culture of individual species. This emerging field, known as metagenomics, enables a survey of the different microorganisms present in a specific environment.[4] Several large-scale projects such as the Human Microbiome Initiative have characterized microbial genomes from hundreds of isolated human symbionts and have shed light on the complex interplay between the human host and its microbial populace, and how this changes in health and disease.

This article aims to discuss the emerging body of knowledge that links the gut microbiome to the development of obesity and metabolic disease. The growing prevalence of overweight and obesity are easily linked to the sedentary lifestyles and calorie-dense diets typical of 'Westernized' countries. There is, however, growing evidence that there are powerful physiological processes that restrict any cognitive mechanisms to reduce excessive weight by drastic changes in lifestyle. The reason is that those same physiological processes maintain body weight within a narrow range.[5] In this respect, obesity is increasingly recognized as a disease rather than as a willful choice.

## THE OBESITY MICROBIOME

The involvement of the gut microbiome in obesity came to light from studies that compared the microbiota between lean and obese mice and human subjects. Using obese, leptin-deficient *ob/ob* mice, Ley *et al* showed a difference in the ratio of the two dominant intestinal phyla – *Bacteroides* and *Firmicutes*, between obese mice and their lean counterparts.[6] The reason for using leptin-deficient mice is that they exhibit relatively mild hyperglycemia and obesity. This seminal paper showed that in mice, kinship is a strong determinant of caecal microbial composition. Furthermore, Ley *et al* showed that regardless of family membership, obesity is associated with a 50% reduction of *Bacteroides* species and a greater proportion of *Firmicutes* relative to lean mice. These findings were reproduced by Ley *et al* in humans[7] and subsequently by other investigators.[8-10] Other investigators have however failed to fully reproduce these findings,[11] possibly due to methodological differences in determining the composition of the microbiome.

Further insight into the role of the microbiome in obesity comes from germ-free (GF) mice. GF mice are born and bred under special conditions to control their exposure to microbes, and can be inoculated by specific bacterial strains for research purposes (gnotobiotics). Studies have shown that GF mice are leaner and resistant to obesity when consuming a high fat, high carbohydrate diet.[12] Subsequently, Backhead *et al* showed that the transfer of caecal bacteria harvested from normal mice to their GF counterparts is accompanied by a 60% increase in body fat content and insulin resistance, despite a reduced fat intake.[13] Turnbaugh *et al* proposed that the gut microbiota of obese individuals are more efficient at extracting calories from the diet when compared to microbes from lean individuals. In a series of elegant experiments, they transferred caecal microbes from obese and lean mice to GF mice, the investigators showed that wild-type GF mice exhibit a greater increase in body fat when colonized by bacteria from obese donors than GF mice colonized by caecal bacteria from lean donors.[14] Similar findings have been reported in human studies, where a randomized controlled trial reported significantly improved insulin sensitivity in male patients with metabolic syndrome who

IN A COHORT OF OVER 28,000 DANISH SUBJECTS, BORN FROM NORMAL WEIGHT MOTHERS, AN EARLY EXPOSURE TO ANTIBIOTICS BEFORE THE 6TH MONTH OF AGE HAS BEEN LINKED TO AN INCREASED RISK OF BEING OBESE LATER ON IN LIFE

received allogenic fecal bacteria from a lean donor compared to those who received an autologous gut microbiota infusion.[15] This study also identified a significant increase in intestinal butyrate-producing bacteria in recipients of microbiota from a lean donor. Comparable results have been reported in two large metagenome-wide association studies.[16-17] Karlson *et al* showed that T2DM is accompanied by a decrease in butyrate-producing *Roseburia* and *Faecalibacterium prauznitzii* when compared to healthy subjects.[16]

## THE EFFECTS OF MICROBIOME-DERIVED PRODUCTS

Butyrate, along with propionate and acetate, are short-chain fatty acids (SCFAs) derived from the bacterial degradation of complex polysaccharides in the gut.[18] They have important metabolic roles, with butyrate acting as a metabolic substrate for colonic epithelial cells. Studies have implicated these SCFAs in the pathogenesis of inflammatory bowel disease (IBD). Vernia *et al* identified low fecal concentrations of butyrate in ulcerative colitis,[19] and butyrate enemas suppress inflammation in distal ulcerative colitis[20] Other studies have investigated the systemic anti-inflammatory effect of butyrate in IBD,[21-22] while Gao *et al* report that oral butyrate administration improves insulin sensitivity and energy expenditure in obese mice.[23]

Butyrate is a histone deacetylase (HDAC) inhibitor. Lysine residues in histone proteins undergo post-translational modification as part of the epigenetic regulation of gene expression. The acetylation of lysine residues in histone proteins leads to nucleosome unfolding and transcriptional activation. Conversely, histone deacetylase removes acetyl groups on lysine in histone proteins, leading to transcriptional repression.[24] Gao *et al* showed that butyrate administration is associated with increased expression of PGC-1α, which leads to increased fatty acid oxidation, mitochondrial activity and energy expenditure.[23] This directly links microbiome-derived SCFA to changes in host gene expression pathways that promote insulin sensitivity.

SCFA also act on host signaling pathways by binding to G-protein coupled receptors in enteroendocrine cells. Butyrate has been shown to trigger production and release of the peptide hormone PYY from intestinal enterocytes.[25] Butyrate is also postulated to play a role in the maintenance of intestinal epithelial integrity, thereby preventing the translocation of endotoxins produced by intestinal Gram-negative bacteria. Obesity and insulin resistance are associated with a chronic subclinical inflammatory response,[26] and studies have shown that high fat diets in mice increase the proportion of endotoxin-producing gut microbes and lead to insulin resistance.[27]

The gut microbiome is intimately linked to the regulation of carbohydrate and lipid metabolism in the host. Specifically, research has shown that butyrate-producing bacteria improve insulin sensitivity in both animal and human subjects,[23,28] T2DM and obesity are also linked to changes in the composition of the microbiome, although evidence regarding the causality of these changes is not clear, for the observed changes in the microbiome might be secondary to the altered intestinal motility and bacterial overgrowth seen in T2DM. Critically, clinical trials involving SCFA supplementation and microbial transfer are needed in order to evaluate any therapeutic application from this emerging field of research.

## THE EFFECT OF HOST FACTORS ON THE GUT MICROBIOME

The widespread availability of antibiotics has resulted in a number of public health benefits and a reduced infectious disease burden. However, a growing body of evidence links antibiotic use to the obesity pandemic.[29] Thuny *et al* link long term (6 week) vancomycin use in infective endocarditis to weight gain in adult males.[30] Short term administration of oral ciprofloxacin has been linked to rapid and permanent changes in the composition and diversity of the gut microbiome.[31] In a cohort of over 28,000 Danish subjects, born from normal weight women, an early exposure to antibiotics before the sixth month of age has been linked to an increased risk of being obese later on in life.[32] These findings reinforce the need for more judicious use of antibiotics, and further emphasize the functional interaction between the gut microbiome and host metabolism.

Host diet is also an important determinant of microbiome composition. Changes in fecal enterotypes, as determined by *Prevotella* and *Bacteroides*, have been shown to occur in response to long term protein-rich vs carbohydrate-rich diets in man.[33]

## CONCLUSION

The gut microbiome has an intimate relationship with the host organism that is vital for energy homeostasis. Studies suggest that changes in microbial composition can lead to obesity through various mechanisms. Although this area of research is still in its infancy, it opens up a number of potential therapeutic approaches to facilitate weight loss or treat obesity and its complications.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

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

Asthma

# Because I simply don't have space for asthma




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

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

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

**Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information**

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

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

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

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

***REPORTING ADVERSE EVENTS (AEs):***

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

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

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

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

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

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

MLT_GIB/RESP/0006/14 Date of preparation: January 2014

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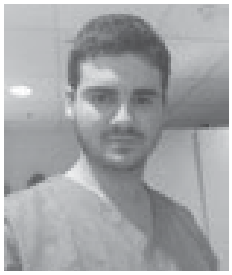
Theravance

# MY EXPERIENCES WITHIN MMSA



GLENN COSTA

It has been over a year now since my admission into Medical School. Back then I was still a greenhorn when it came to understanding and appreciating the various extra-curricular activities that MMSA had to offer. Now that I am in my second year of pre-clinical study, I can easily say that MMSA is not only one of the most active student organisations on campus but also serves as a crucial ingredient in the recipe of success for any medical student.

The annual Word Diabetes Day happened to be my first experience as an active member of the organisation. My first health checks were truly memorable as they shed light on my actual life aspirations – that of helping and interacting with those in need.

Later on throughout the academic year, I started to participate in a myriad of events organised by the different standing committees .What fascinated me the most was the fact that although the various committees have different functions, they all share a common goal – that of creating better doctors and educating the general populace.

Participating in events such as the Training Resource and Development Programme, Medic T and the various workshops held on a monthly basis gave me more insight on the various active roles that a student can assume within the MMSA and what personal qualities would be ideal for that particular role.

During the summer recess, I enrolled as an active member in the Finance Team as an External Financial Assistant. I was responsible for obtaining sponsors from various companies and liaising with members of the standing committees within the MMSA. Direct communication with large commercial businesses as well as working in a team setting proved to be very fruitful and greatly enhanced my personality as well as my communication skills which are paramount for my future career.

To sum up, I cannot but thank MMSA for giving us students the opportunity to achieve our full potential in becoming the country's doctors of tomorrow. To this day, I am still discovering new experiences which MMSA has to offer.

# ALCOHOLISM IN THE COMMUNITY

TRICIA MICALLEF

The misuse of alcohol resulted in 2.5 million years of potential life lost each year in the United States from 2006 – 2010.[1] Consequences of alcohol misuse arise in the form of acute and chronic conditions, together with adverse social consequences and possible drunk-driving accidents. It, therefore, stands to question what health care professionals can do in order to reduce the above statistic. Firstly, we should act as role models and not partake in such activities of alcohol abuse in our free time. Additionally, we must educate our patients on the serious adverse effects that could result from alcoholism.

*But how does one recognise alcoholic patients in the community?*

Since the diagnosis of alcoholism depends on the drinker being willing to honestly answer a series of uncomfortable questions about his or her drinking habits, this can be a delicate situation, particularly because a common symptom of alcoholism is denial.

Essential points to consider when discussing alcoholism, be it with the patient themselves or their loved ones, include the importance of alcohol to the person, the amount of alcohol consumed and the frequency of hangovers and blackouts.

The use of alcohol as a mood enhancer or coping mechanism is common amongst alcoholics, as are promises on cutting down alcohol-intake, which remain unfulfilled. Tolerance to considerable amounts of alcohol with very few signs of intoxication particularly in conjunction with the compulsion to finish every drink, including others' drinks should raise alarms.

It is imperative to note that many alcoholics can maintain the outward appearance of a normal life while drinking to excess, until a specific unfortunate life event occurs, such as being left by their partner. This must be kept in mind when determining the presence of alcoholic-tendencies in a patient.

REFERENCE

1. Stahre M, Roeber J, Kanny D, Brewer RD, Zhang X. Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. Prev Chronic Dis 2014;11:130293.

# Symbicort® Turbohaler®

(budesonide/formoterol)

Easy to use[1]

Patients do not need to hold their breath after inhalation


High lung deposition (25-40% of delivered dose)[2]

Peak Inspiratory Flow from around 30 L/min[3]

## Symbicort® Turbohaler® – For Asthma and severe COPD

Consult SmPC for full information

Symbicort Turbohaler

ABRIDGED PRESCRIBING INFORMATION. Refer to Summary of Product Characteristics (SmPC) before prescribing. Symbicort*Turbohaler*100 micrograms/6 micrograms/inhalation, inhalation powder Symbicort*Turbohaler* 200 micrograms/6 micrograms/inhalation, inhalation powder (budesonide/formoterol fumarate dihydrate) Indication Asthma: Treatment of asthma where the use of a combination (inhaled corticosteroid and long acting β2 adrenoceptor agonist) is appropriate. Symbicort Turbohaler 100/6 is not appropriate for patients with severe asthma. COPD (*Symbicort 200/6 only*): Symptomatic treatment of patients with COPD with FEV1 <70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy. **Presentation** Inhalation powder. *Symbicort Turbohaler 100/6*: Each metered dose contains 100 mcg budesonide/inhalation and 6 mcg formoterol fumarate dihydrate/inhalation. *Symbicort Turbohaler 200/6*: Each metered dose contains 200 mcg budesonide/inhalation and 6 mcg formoterol fumarate dihydrate/inhalation. Refer to the SmPC for information on the method of administration. Dosage and Administration Asthma Not intended for the initial management of asthma. Dose should be individualised. If a patient requires dosages outside recommended regimen, appropriate doses using individual inhalers should be prescribed. When long-term symptoms are controlled, titrate to the lowest effective dose, which could include a once daily dosage. Symbicort **maintenance therapy – regular maintenance treatment with a separate rescue medication:** *Adults (≥18 years, including elderly)*: 1-2 inhalations twice daily (maximum 4 inhalations twice daily). *Adolescents (12-17 years)*: 1-2 inhalations twice daily. *Children 6-11 years (Symbicort 100/6 only)*: 2 inhalations twice daily. *Children under 6 years*: Not recommended. **Symbicort maintenance and reliever therapy – regular maintenance treatment and as needed in response to symptoms**: consider for patients with (i) inadequate asthma control and in frequent need of reliever medication (ii) previous asthma exacerbations requiring medical intervention. *Adults (including elderly)*: 1 inhalation twice daily or as 2 inhalations once daily. 2 inhalations twice daily may be appropriate for some patients (200/6 strength only). Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, up to 12 inhalations a day could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice and should be reassessed; their maintenance therapy should be reconsidered. Patients should be advised to always have Symbicort for reliever use. *Children and adolescents under 18 years of age:* not recommended. *COPD (Symbicort 200/6 only): Adults (≥ 18 years)*: 2 inhalations twice daily. Contraindications Hypersensitivity to active substances or excipient. Warnings and Precautions If treatment is ineffective, or exceeds the highest recommended dose therapy should be reassessed. Sudden and progressive deterioration in control requires urgent medical assessment. Treatment should not be stopped abruptly. Patients should have their appropriate rescue medication available at all times i.e. either Symbicort or a separate reliever. If needed before exercise a separate reliever should be used. Therapy should not be initiated during an exacerbation. Serious asthma-related adverse events and exacerbations may occur. If asthma symptoms remain uncontrolled or worsen patients should continue treatment but seek medical advice. If paradoxical bronchospasm occurs Symbicort should be discontinued. It responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Systemic effects may occur, particularly at high doses prescribed for long periods e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Height of children should be monitored. Potential effects on bone should be considered especially in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress e.g. severe infections or elective surgery. Transfer from oral steroid therapy to Symbicort may result in the appearance of allergic or arthritic symptoms which will need treatment. In rare cases, tiredness, headache, nausea and vomiting can occur due to insufficient glucocorticosteroid effect and temporary increase in the dose of oral glucocorticosteroids may be necessary. To minimise risk of oropharyngeal candida infection patients should rinse mouth with water. Observe caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, or severe cardiovascular disorders. Re-evaluate need for Symbicort in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways. Hypokalaemia may occur at high doses. Particular caution recommended in unstable or acute severe asthma. Monitor serum potassium levels. In diabetic patients consider additional blood glucose monitoring. The small amounts of milk proteins present may cause allergic reactions. Drug Interactions Concomitant treatment with potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration should be as long as possible. Symbicort maintenance and reliever therapy is not recommended in these patients. Not recommended with beta adrenergic blockers (including eye drops) unless compelling reasons. Concomitant administration with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) and TCAs can prolong the QTc-interval and increase the risk of ventricular arrhythmias. L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance. Concomitant administration with MAOIs, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertension. Elevated risk of arrhythmias in patients receiving anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the disposition towards arrhythmias in patients taking digitalis glycosides Fertility, Pregnancy and Lactation No data available on the potential effect on fertility. During pregnancy, use only when the benefits outweigh the potential risks. Budesonide is excreted in breast milk, however at therapeutic doses no effects on the child are anticipated.

Undesirable effects *Common*: headache, palpitations, tremor, Candida infections in the oropharynx, coughing, mild irritation in the throat, hoarseness. *Uncommon*: tachycardia, muscle cramps, nausea, dizziness, bruises, aggression, psychomotor hyperactivity, anxiety, sleep disorders. *Rare*: hypokalaemia, cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles, bronchospasm and immediate and delayed hypersensitivity reactions including exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction. *Very Rare*: depression, behavioural changes (predominantly in children), angina pectoris, prolongation of QTc-interval, hyperglycaemia, taste disturbance, Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, cataract, glaucoma and variations in blood pressure. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. Package Quantities Each Symbicort Turbohaler contains 120 inhalations. Legal Status POM. Marketing Authorisation Numbers MA 046/00901-2. Marketing Authorisation Holder (MAH) AstraZeneca AB, Gartunavagen, S-151 85 Sodertalje, Sweden. Further product information available on request from Associated Drug Company Limited, Triq l-Esportaturi, Mriehel, Birkirkara BKR 3000, Malta. Tel: (+356) 2277 8115. Abridged Prescribing Information prepared 12/15. Symbicort and Turbohaler are trademarks of the AstraZeneca group of companies. URN No: 13/0125 Date of Preparation: January 2016

AstraZeneca Respiratory

**Reference: 1.** Adelphi Respiratory Disease Specific Programme 2009. **2.** Olof Selroos et al. *Treat Respir Med* 2008; 5 (5): 305-315. **3.** Engel et al. Br J Clin Pharmacol 1992; 33(4): 439-44.

# Augmentin® ES

**600 mg/42.9 mg/5 ml**

## Amoxicillin/Clavulanate Potassium

## Powder for oral suspension


- ✓ Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- ✓ Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- ✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- ✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

# *Spreading infectious energy!*

**Mini Abridged Prescribing Information:** *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PRESENTATION:** 600 mg/42.9 mg/5 ml powder for oral suspension. Supplied in 100 ml glass bottle with a dosing spoon. **INDICATION:** treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. **POSOLOGY & ADMINISTRATION:** Oral use. Recommended dose is 90/6.4 mg/kg/day in two divided doses. To minimise potential gastrointestinal intolerance, administer at the start of a meal. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to SPC's for full list of undesirable effects*. **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2014. **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).** ***REPORTING ADVERSE EVENTS (AEs):*** **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). **Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

**References:**

1. Anthony R. White *et al*. Augmentin® amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent Journal of Antimicrobial Chemotherapy (2004) 53, Suppl. S1, i3–i20.
2. Gilbert DN, *et al*. Sanford guide to Antimicrobial Therapy v.3.11 – last updated March 11, 2014. Sperryville; Antimicrobial Therapy, Inc. 2014.
3. Lieberthal AS *et al*. The Diagnosis and Management of Acute Otitis Media. Pediatrics. 2013; 131; e964 Epub 2013 Feb 25.
4. Augmentin ES Summary of Product Characteristics, May 2015.

Prepared: September 2015
Job No: MLT_GIB/AES/0001/15(2)

CLAYTON JOHN FSADNI, SARAH CARUANA GALIZIA & MOROLAYO OWOLABI



# COLONOSCOPY SCREENING IN MODERATE-RISK FAMILY GROUPS


## ABSTRACT

Colorectal cancer is one of the commonest forms of cancer in the Maltese population. It can be treated successfully if detected early. Education and screening are the major components of early detection. The aim of this study was to determine the pattern of colonoscopy screening in patients at moderate risk of developing colorectal cancer in a surgical firm at Mater Dei Hospital. 90 patients that fit into the moderate-risk category were identified from the firm's endoscopy database. The pattern of screening was then compared to the NICE guidelines. It was found that colonoscopy screening was more aggressive than recommended by the NICE guidelines.


## INTRODUCTION

Colorectal cancer (CRC) is one of the commonest cancers in the Maltese population but can be treated successfully if detected early. The major components of early detection are education and screening.[1]

People with a family history of CRC but with no genetic disorder putting them at high risk of CRC are considered to be at moderate risk of developing CRC. These are further divided into high/moderate and low/moderate-risk subcategories. The preferred surveillance mode for patients with a moderate risk of developing CRC is total colonoscopy.[2]

The aims of this audit are to:

- Evaluate the colonoscopy screening pattern for individuals with a family history indicating moderate risk for CRC in a surgical firm at Mater Dei Hospital.
- Compare this pattern with that recommended by the NICE guidelines.

## METHODOLOGY

### SETTING AND DATA COLLECTION

This retrospective study was conducted at Mater Dei Hospital between April - June 2015 within a surgical firm that records its endoscopic services on iSOFT, which is a secure database utilised at Mater Dei Hospital.

A total of 90 patients having one or more first degree relatives (FDRs) affected by colorectal cancer who had undergone at least one colonoscopy between November 2007 - January 2015 were identified. Their respective age, indication for colonoscopy, date of procedure and findings were retrieved from the database.

These patients were then phoned and asked about:

1. The number of relatives and degree of relation of relatives affected by CRC;
2. Age of relative/s at time of diagnosis with CRC;
3. Presence of gastrointestinal - related symptoms prior to colonoscopy;
4. Number of colonoscopies and the respective dates at which they were performed;
5. Any other investigative procedures done for the same condition.

A summary of the NICE guidelines for colorectal cancer screening and surveillance is shown in Table 1. Compliance for each parameter was awarded a 25% score. Compliance to all categories was given a 100% compliance. The average percentage compliance was then calculated for all patients within each risk category. Any discordance between the guidelines and actual practice was recorded.

| | Moderate risk family history categories | Screening Procedure | Age at initial screen | Screening Procedure and interval |
|---|---|---|---|---|
| High Moderate Risk Category | Colorectal cancer in 3 *FDR in first degree kinship, none < 50 years | Colonoscopy | 50 years | 5 yearly colonoscopy to age 75 years |
| | Colorectal cancer in 2 FDR in first degree kinship, mean age < 60 years | Colonoscopy | 50 years | 5 yearly colonoscopy to age 75 years |
| Low Moderate Risk Category | Colorectal cancer in 2 FDR ≥ 60 years | Colonoscopy | 55 years | Once-only colonoscopy at age 55 years. If normal – no follow up. |
| | Colorectal cancer in 1 FDR < 50 years | Colonoscopy | 55 years | Once-only colonoscopy at age 55 years. If normal – no follow up. |
| All other Family history of colorectal cancer | All other family history of colorectal cancer | Colonoscopy | N/A | N/A |

Table 1: Summary of NICE Guidelines for colorectal cancer screening and surveillance in moderate risk family groups. *FDR = First Degree Relative.

Source: Cairns SR, Scholefield JH, Steele RJ et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010; 59(5):666-690

## STANDARD USED

The guidelines used were the NICE Guidelines for colorectal cancer screening and surveillance in moderate-risk family groups.[2] These were updated by The British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) in 2002.

## DATA ANALYSIS

All data were processed using Microsoft Excel 2013 and analysed by comparing the number of colonoscopies performed between November 2007 - January 2015 for every patient, with the screening procedure and respective interval recommended by the NICE Guidelines.[2] The parameters required to assess compliance with guidelines included:

1. The number of first degree relatives affected;
2. Age of diagnosis of such relative/s;
3. Age of patient at which colonoscopy was first undergone;
4. Number of colonoscopies within a 5-year interval.

Any discordance between the guidelines and actual practice was recorded.

## ETHICAL APPROVAL AND CONSENT

The study was approved by the Audit and Data Protection Act Committee and the Mater Dei Hospital data protection Unit. Consent was obtained from the Consultant Surgeon of the Firm.

## RESULTS

As shown in Figure 1 the greatest number of patients fell in the 'other Family history of CRC category', (35 from 90 patients; 39%). Average compliance to the NICE guidelines was greatest in the low/moderate-risk category (75%) while the lowest compliance was observed in the other family history of CRC category (25%), as shown in Figure 2.

There was 100% compliance in all categories to the NICE recommendations pertaining to the screening process of patients with FDR having a history of CRC (Table 2). Compliance to mean age at which relatives were diagnosed with CRC was 100% in the high/moderate-risk and low/moderate-risk categories. All the patients screened had one or more first degree relatives with history of colorectal cancer, so compliance to this parameter was fulfilled in all categories. The mean age at which the affected relatives were diagnosed with colorectal cancer was also complied with in the low/moderate-risk category and high/moderate-risk category. However, compliance to the recommended frequency of screening and age at which to start screening was low in all categories. Overall percentage compliance to the NICE guidelines across all categories was 11% (Figure 3).

## DISCUSSION

### FAMILY HISTORY CATEGORIES AND RECOMMENDATIONS

A positive family history of CRC confers an increased risk for the development of CRC.[3]

The study considered the moderate-risk category which is further divided into high/moderate-risk and low/moderate-risk. The remaining patients fell into the 'other family history of CRC' category.

***i. The high/moderate-risk category[1] includes:***

1. Patients with 3 or more affected relatives in a first degree kinship with each other (none <50 years old as otherwise they would fulfil high risk criteria).
2. Two affected relatives with a mean age <60 years in a first degree kinship.

*Recommendation*

In this category patients merit low intensity surveillance comprising 5-yearly colonoscopy commencing at age 50 and continuing till 75 years of age. Polyps must be snared and histologically characterised. If adenomas are present, surveillance should be instigated as per adenoma surveillance guidelines.[2]

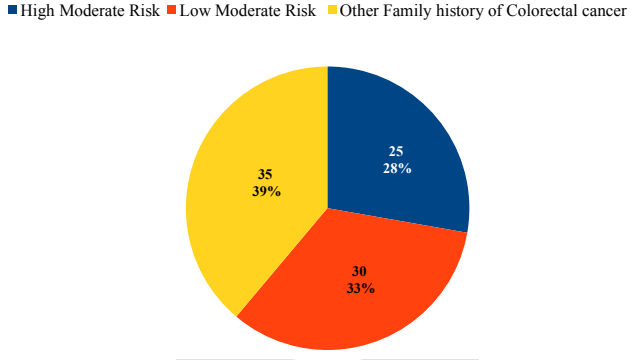
***ii. The low/moderate-risk category[1] includes:***

1. Patients with only one affected relative <50 years old.
2. Patients with only two affected first degree relatives aged 60 years or older.

*Recommendation*

Once only colonoscopy at 55 years of age. Polyps must be snared and histologically characterised. If adenomas are present surveillance should be instigated as per adenoma surveillance guidelines.[2]

**Figure 1.** Number and percentage of patients in each moderate risk category




| | Compliance to presence of FDR with History of CRC | Compliance to Mean age at which relative was diagnosed with CRC | Compliance to number of colonoscopies performed within 5 years | Compliance to Age of First Colonoscopy |
|---|---|---|---|---|
| High moderate risk | 100% | 100% | 20% | 20% |
| Low moderate risk | 100% | 100% | 33% | 50% |
| Other family history of colorectal cancer | 100% | N/A | N/A | N/A |

Table 2: Compliance to the presence of FDR with history of CRC, mean age at which relative was diagnosed with CRC, the number of colonoscopies performed within 5 years and the age at which first colonoscopy was performed in the 3 moderate risk categories.

### *iii. All other family history of CRC*[1]

*Recommendation*

No need for screening.

## COMPLIANCE WITH SCREENING RECOMMENDATIONS

Most patients screened had a family history of CRC but did not fit the criteria for low or high moderate-risk. The highest average percentage compliance (75%, n=22.5) was found in the low/moderate-risk category (Figure 2).

### *a. Compliance in the High/Moderate-Risk Category*

In the high/moderate-risk category, full compliance was observed with regards to the NICE criteria relating to the screening of patients that had first degree relatives with a history of CRC as well as the mean age at which the relatives were diagnosed. Compliance was not observed with regard to the number of recommended colonoscopies as there was a tendency to screen every 2 years rather than the recommended 5-year interval. When it came to the age of first colonoscopy, delayed and early screening initiation were equally observed. Unawareness of the guidelines, practice of defensive medicine and pressure from patients could all be reasons for non-compliance.

### *b. Compliance in the Low/Moderate-Risk Category*

Most patients in this category had more colonoscopies than recommended by the guidelines. Reasons for this may be similar as for the high/moderate-risk category, that is inadequate history taking leading to improper categorisation of patients, unawareness of the guidelines and the practice of defensive medicine by the clinician. Pressure from the patient and/or relatives, mainly due to anxiety and insecurity may also have contributed to this.

With regards to the age at which screening was initiated, non-compliance was due to delayed screening initiation rather than early screening initiation. Delayed screening initiation may occur if the patient is not under the care of a primary health care provider at the time at which screening is supposed to start. Primary health care providers have an important role to play in advising patients when they should have their first screening colonoscopy as advised by guidelines and according to which risk category they are in. Another reason for delayed screening initiation is that the patient may be older than the recommended age for screening initiation by the time CRC is discovered in his/her relatives. Health care providers' lack of knowledge of the screening guidelines may also contribute to delayed screening initiation.

### *c. Compliance in Patients with 'Other Family History of CRC'*

According to the NICE guidelines, screening is not recommended for those patients with a family history of CRC that did not fall into either of the above categories. Hence, these patients should not have had a colonoscopy. The study showed that screening was mainly conducted on the basis of whether the patient had a first degree relative with a history of CRC or not. The main reasons for non-compliance in this category are the same as the ones mentioned for the previous categories, that is, limited sampling units, pressure to perform screening by the patient or relatives, the practice of defensive medicine and the possible belief of some clinicians that the guidelines for screening are not stringent enough and that following them may lead to missed cases of CRC.

As for any other guidelines, dissemination, accessibility, clarity and regular updating of guidelines is essential to ensure clinician awareness and to improve compliance.

## OUTCOMES OF THE SCREENING COLONOSCOPIES PERFORMED

Across all categories, in 50% (n=45) of the colonoscopies carried out, no abnormality was detected (Figure 4).

Of the patients that did not fall into low or high/moderate-risk categories, only 14% had polyps on colonoscopy. This supports the recommendation of the guidelines that screening is not to be performed in this category of patients.

It is suggested that left-sided hyperplastic colonic polyps (generally within the reach of a screening sigmoidoscopy) serve as a marker for neoplastic polyps.[4]

**Figure 2.** The average percentage of compliance in each moderate risk category

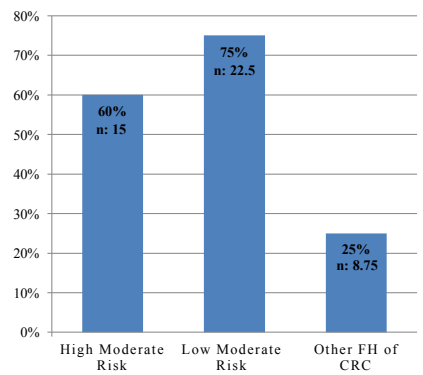
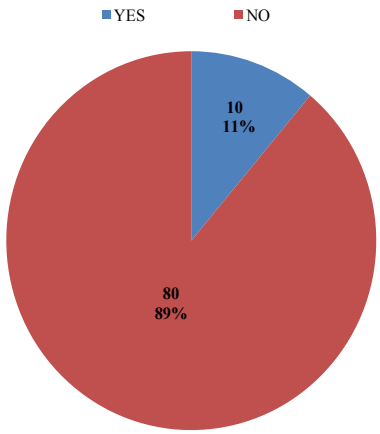
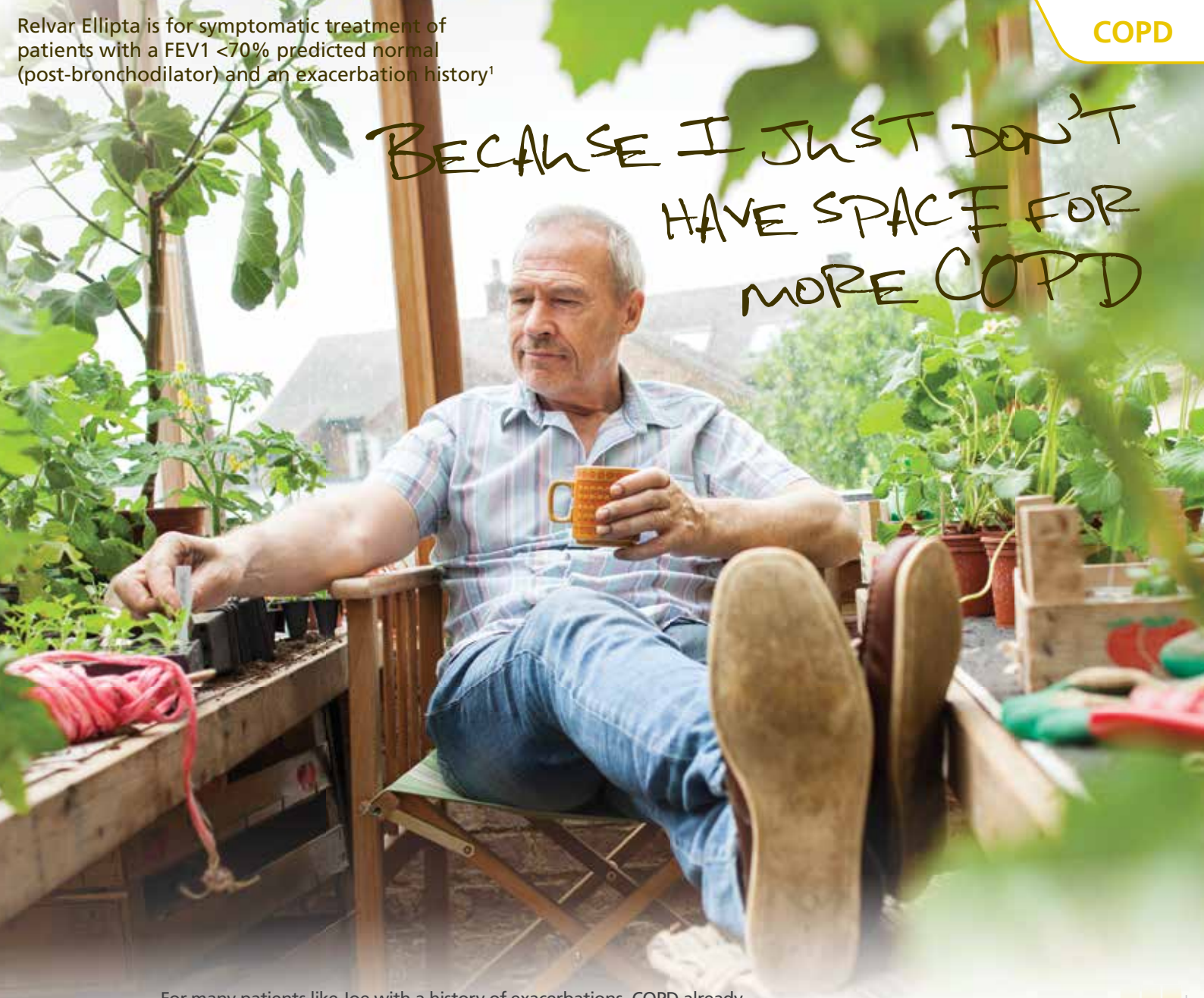



**Figure 3.** Overall compliance to the NICE guidelines



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




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

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

RELVAR® ELLIPTA®

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

**Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information**

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

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

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

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

***REPORTING ADVERSE EVENTS (AEs):***

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

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

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

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

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

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

MLT_GIB/RESP/0007/14 Date of preparation: January 2014

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## LIMITATIONS

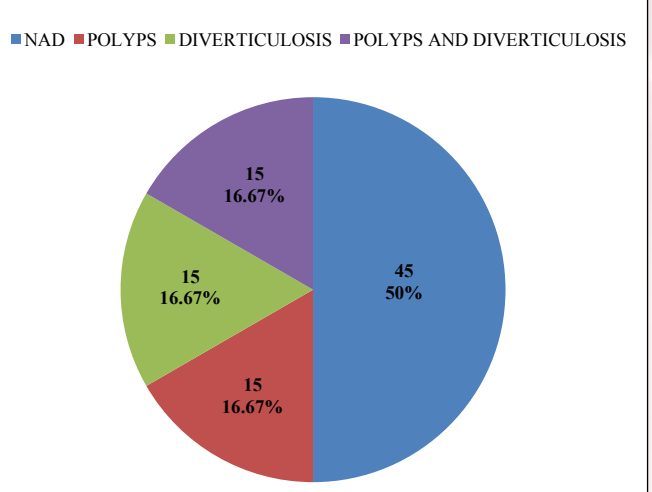
The main limitations were:

a. The cohort of patients all belonged to the same surgical firm;
b. The small sample size;
c. The patients may have forgotten certain details by the time of interview;
d. Time constraints limited the assessment of the overall survival in all referrals according to their risk category.

## CONCLUSION AND RECOMMENDATIONS

The tendency is to screen more aggressively than recommended by the NICE guidelines, possibly due to inaccurate history taking and improper patient categorization, unawareness of the guidelines, the practice of defensive medicine and pressure from anxious patients and relatives. To improve compliance, it is recommended that the NICE guidelines should be easily accessible, clear, well-disseminated and regularly updated. There should be more clinician awareness of the unnecessary stress, inconvenience and discomfort that excessively aggressive screening can cause to patients. In patients that fell into the 'other family history of CRC' category, polyps were only found in 14%, supporting the guidelines' recommendation that screening is not necessary in these patients.

**Figure 4.** Outcome of colonoscopies performed




REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

# GERMAN-MALTESE MEDICAL SOCIETY UPDATE

## SIGNING OF MOU BETWEEN THE MINISTRY OF ENERGY & HEALTH AND RED CROSS HOSPITAL

Also present at the signing of the memorandum were Prof. Dr Rudolf Hesterberg Medical Director, Mr Michael Gribner CEO and Mr Christian Collard Human Resources Manager at RCH

A delegation from Malta visited the Red Cross Hospital (RCH) in Kassel, Germany on the 14th of December to review an ongoing co-operation and to discuss areas in which further co-operation can be carried out. Accompanying his Excellency Mr Albert Friggieri, who in his capacity as Maltese ambassador in Germany had already visited the RCH, there were Dr Chris Fearne, Parliamentary Secretary of the Maltese Ministry of Energy & Health (MEH), Dr Ray Galea, Head of Specialist Medical Education at the University of Malta, and Dr Antoinette Calleja Director of International Relations at the MEH. In addition to the successful Clinical Clerkship Project for Maltese medical students which started in 2013, further expansion in other fields are planned, including specialist exchange in the sphere of medical technical services. Within the framework of this visit an agreement was signed by the MEH of Malta and the RCH with a view to reach these objectives.

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

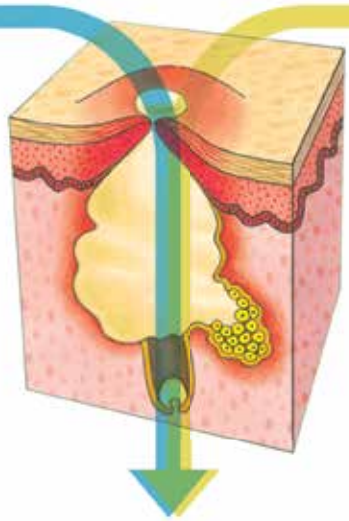
## DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

- Keratolytic[2]
- Treats comedones[2] and inflammatory lesions[5]
- Bactericidal action against *P. acnes* strains[2]

Clindamycin

- Suppresses *P. acnes* [2]
- Anti-inflammatory action[5]



**Duac:[2]**
**Unblocks follicles**
**Reduces inflammation**
**Kills bacteria**
**Reduces the potential for bacterial resistance**

**DUAC UNDERSTANDS WHAT'S IMPORTANT TO PATIENTS**

- **Duac works fast, starting to work in just 2 weeks[3]**
- **Duac is a once daily treatment[2]**
- **Duac is generally well-tolerated[2,5]**


Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

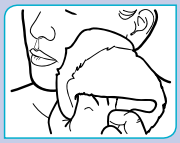
## DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[1]

## YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[4]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin



• Gently pat dry

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

**TIPS[4]**

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

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

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

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

**Local Presentation:** 30g gel. **Marketing Authorization Holder:** GlaxoSmithKline UK Ltd., Trading as Stiefel. **Marketing Authorization Number:** MA 300/01401. **Legal Category:** POM.
**Date of Preparation:** January 2016

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**References: 1.** Langner A *et al.* BJD 2008; **158**: 122–129. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Langner A *et al.* JEADV 2007; **21**: 311-319. **4.** Duac 5% Patient Information Leaflet, October 2014. **5.** Lookingbill DP *et al.* JAAD 1997; **37**: 590-595.

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

# STAR TREK SYMPOSIUM 2016

The Star Trek academic symposium will to be held at the Faculty of IT, UOM between 15-16th July 2016. This event will be a platform for academics from across many disciplines and Star Trek fans to meet and explore the intersection of the humanities and the sciences. There will be inspirational presentations from national and international speakers, with the programme tailored to attract a wide audience. Contributors will be encouraged to explore and present contemporary issues in medicine, science and technology as well as philosophical, psychological and sociological issues relating to the humanities with a specific focus on and a direct correlation to Star Trek.

*The following is a link to the website which is continuously updated with new information:* *startreksymposium.com*



# TOXICOLOGY IN THE MOVIES: 'ERIN BROCKOVICH'

MICHELLE MUSCAT
MD MRCS(ED) MSc

*Erin Brockovich* is a very poignant movie which highlights medical issues in relation to environmental toxicology, specifically hexavalent chromium. Hexavalent chromium is a genotoxic carcinogen that was found to be contaminating drinking water in Hinkley, California.

The dramatized events narrated in this award winning movie are based on a true story. The character of Erin Brockovich is portrayed by the famous actress Julia Roberts. She is the unemployed mother of three children, desperately looking for a job. Eventually, she manages to take up an assistant position at a legal office. The index case is first presented to the viewer when we see her go through a set of laboratory results and later conduct a home visit to better understand the situation. In the movie, Donna Jensen (Marg Helgenberger) tells her that their medical bills are being taken care of by the Pacific Gas and Electric company who had also offered to buy her house. Soon after, we see her speak to a toxicologist who explains to her that there is a difference between, for example, trivalent chromium (Cr(III)) and hexavalent chromium (Cr(VI)), the latter being highly toxic and carcinogenic. An example of hexavalent chromium's practical use is for its anticorrosive properties. The Hinkley chromium level in water exceeded the maximum contaminant level stipulated by regulation. The fictitious Jensen family are said in the film to have had Hodgkin's lymphoma, uterine cancer, chronic nosebleeds etc. Erin Brockovich later meets another family, who used to live across the road to the index family, who had five miscarriages. As the story progresses she meets many more families in the area who were also affected.


**Director:** Steven Soderbergh
**Writer:** Susannah Grant
**Stars:** Julia Roberts, Albert Finney, David Brisbin
**Runtime:** 131 min
**Release date:** 2000
**Awards:** 32 wins and 57 nominations

Hexavalent chromium exposure, such as in this case, also forms part of the wider remit of ecotoxicology and occupational medicine, and remediation strategies have been devised.[1,2] The effects of exposure to hexavalent chromium can be diverse, and have also been studied in cell lines and animal models.[3-8]

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

# ISLAND HOPPING & PUBLIC HEALTH

**MARIKA AZZOPARDI SPEAKS TO DR GAUDEN GALEA, A PUBLIC HEALTH PHYSICIAN WHO IS THE CURRENT DIRECTOR OF THE DIVISION OF NONCOMMUNICABLE DISEASES AND PROMOTING HEALTH THROUGH THE LIFE COURSE AT THE WORLD HEALTH ORGANIZATION REGIONAL OFFICE FOR EUROPE, BASED IN COPENHAGEN.**

**TS: You are presently living and working in Copenhagen - can you explain more about this post?**

I have been employed with WHO since 1998 and this is my 4th duty station to date. I started off with two years in Fiji, then six years in Manila, then four years in Geneva and have now been in Copenhagen for five years.

**TS: What was your specialisation in Malta before you left?**

I specialized in public health and held two posts. The first was Head of the Health Education Unit, which is now incorporated into the Health Promotion & Disease Prevention Services. I spent six years in this post. Afterwards I became the first Executive Director of the Institute of Healthcare, now Faculty of Health Sciences. I held this post between 1992 and 1998.

**TS: How did you come to relocate abroad?**

The public health discipline is characteristically dependent on social, cultural, behavioural and other determinants of health and disease, all of which are often connected with international influences. Consider, for instance, migration, disease outbreaks, cultural influences such as advertising, trade and cross-border relations ... it is all much larger than what happens in a single country. In Malta, I was very aware of the influences of public health on small island nations. In fact, Malta is a key leader in the study of sociology, economics, administration, and public health amongst small island nations. I began writing about the topic and presented a paper to the WHO. That basically started it all.

**TS: What has been your most pleasantly surprising experience during these years?**

Living in the small islands of the Pacific. I was offered the post in Suva, Fiji at the end of 1997, to manage a programme called 'Healthy Islands' which concerned itself with non-communicable epidemics. It was a very different context to Malta, of course. I was pleasantly surprised to find a good level of technical competences and much of my Maltese experience in public health was directly relevant to the work I conducted there.

*With Dr Shichuo Li in the Palais des Nations, Geneva. Dr Li was Dr Galea's director in Fiji*

**TS: Can you explain more?**

In the mid-late 1990's the Pacific islands started exploring health promotion. I was lucky to be given the chance to contribute to a number of initiatives. By 1998, several projects were running in parallel and I had the chance to work in Fiji, Tonga, Papua New Guinea, Nauru, Marshall Islands, Cook Islands, Samoa, Micronesia and others. I travelled to 13 of the 22 Pacific countries and territories. Epidemiological studies showed very high levels of risk and burden related to a number of noncommunicable diseases. This meant that one had to take into account health systems, trade patterns and behavioural influences, alongside genetic and demographic issues. Consider the presence of certain types of imported foods - turkey tails and mutton flaps – which are all extremely high in fats and which, over a relatively short time period, came to form part of "traditional food". Furthermore, fishing rights are leased as a source of foreign revenue. This led to a situation, where ironically, island people primarily accessed canned fish, rather than atolls and the sea. These trends (among other influences) resulted in a high incidence of diabetes, obesity and heart disease which exerted a toll on services, well-being and life expectancy. I must say that during these years I was privileged to work with many leaders who guided the islands in the implementation of innovative programmes to combat such a situation.

**TS: What about your present role in Europe?**

I am Director of Noncommunicable Diseases and Promoting Health through the Lifecourse within the Regional Office of Europe at the WHO. Briefly, my division covers the fifty-

*Reaching agreement with Dr Vassily Zharko, Minister of Health of Belarus, on the organisation of a European Conference in Minsk*

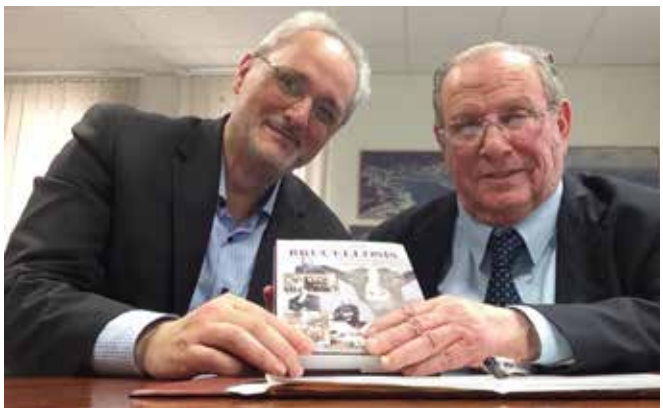
three Member States of Europe, ranging from Central Asia to Western Europe. Technical units under NCDs include tobacco and alcohol control, diet and physical activity, NCD management, mental health and the prevention of violence and injury. Under the life-course programme, an area that was the subject of a Ministerial Conference in Minsk, Belarus in 2015, we cover the gamut from neonatal health to healthy ageing. A fairly broad remit in a very diverse Europe.

**TS: What was it like, travelling and relocating in such different surroundings?**

There were definitely plenty of radical lifestyle changes, actually less dramatic than one might think. I moved with my wife, Ann, who is also a physician and our two children; with a family, adjustments are not always simple. However, it was all a very enriching experience. We researched each location, searched the best schooling at every level and with careful planning, managed it all. These are normal experiences to many of my peers who are expatriate.

**TS: Let us move away from the islands for a moment and concentrate on your involvement here in Malta with the set-up of *The Synapse*. What are your memories on that?**

It all began as a joint partnership with Dr Wilfred Galea. We were young medical doctors interested in programming and IT. The technology was very limited back then, as was the awareness of the medical community on the riches of the World Wide Web. We wanted to change that and provide available resources to medical students and professionals. Our plan was to kick off the project with a bulletin board, carrying info such as Department of Health circulars, for instance. The idea of a bulletin board was suddenly overtaken by the introduction of Internet in Malta. We found we could run our own server and the new technology proved to be a huge but rewarding learning curve for us. Wilfred built a network of contacts with colleagues and companies, whilst I tackled web development and design. *The Synapse* embraced new partners such as Keith Gauci and Aldo Calleja who took on the management and technical side of the project. I had to leave the partnership when I moved abroad. I am happy to see the project progressed successfully thanks to Wilfred's able guidance. Truly, those early days in our discovery of the potential of the internet were extremely exciting for us. Since then, I have kept abreast with technology, including the exploration of new languages and recent trends towards "big data", data visualisation, machine learning, and becoming familiar with a range of open source statistical computing software … all tools which have the potential to transform the face of public health itself.



*With Prof John Rizzo Naudi, Chairman of the Institute of Health Care. Dr Galea was Executive Director at the Institute*

## I READ THE SYNAPSE BECAUSE...

Mostly for the nostalgia of remembering where we started, and am pleased to see, on occasional visits, that *The Synapse* is still going strong, that it has incorporated new channels – print, web and app – and that it is still providing a sterling service to the profession.

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| 02MML | 02MMR | 7.5 – 11 | 9 – 12.5 | M |
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# ULTRASOUND DIAGNOSIS OF COMMON MUSCULO-SKELETAL DISORDERS IN YOUNG ATHLETES – PART I

PIERRE VASSALLO

Ultrasound (US) has become the most commonly used imaging method to assess musculo-skeletal (MSK) injuries. In addition to the high soft tissue image quality it provides, MSK US has the advantage of providing a rapid mode of evaluation that avoids the use of ionising radiation, allows dynamic assessment and can guide targeted treatment. Use of high quality scanning equipment to diagnose and treat MSK injuries is of the utmost importance. Without the necessary high image resolution, most injuries will be missed. Sonographer experience also has a major influence on diagnostic accuracy.

In children, tendons and ligaments are usually stronger than the growth plate. Thus, growth plate injuries are more common than tendonous/ligamentous injuries. Consequently, overuse injuries in a tendon that attaches to an un-united apophysis are more likely to affect the apophysis than the tendon. Such injuries were previously referred to as osteochondrites or apophysites, however they are now recognised as overuse injuries. The most common type of apophyseal overuse injury is Osgood-Schlatter's disease (OSD), which affects the insertion of the patellar tendon into the tibia. In the past, a child or young adult presenting with pain below the patella would promptly be referred for a lateral X-ray of the knee (Fig 1a) to detect OSD. Today, an ultrasound of the knee will not only depict the fragmented ossification centre seen on X-ray, but will also provide more detailed information on the state of the soft tissues, including the presence of any fluid collections or adventitial bursae, while confirming or otherwise the integrity of the patellar tendon (Fig 1b).

Other common sites of apophyseal injury include the proximal patellar tendon insertion (Sinding-Larsen-Johansson's disease) (Fig 2), the insertion of the Achilles' tendon into the calcaneus (Sever's disease) (Fig 3) and the insertion of the triceps muscle into the olecranon.

In adolescents, after growth plate closure, injuries at tendon attachment sites are generally referred to tendinopathies; the term tendinopathy refers to a combination of pathologies that include tendinosis (collagen degeneration, fibre disorientation and accumulation of mucoid substance), tendinitis (findings of tendinosis and the presence of inflammatory cells) and paratendinitis (inflammation of the paratenon). Unlike MRI, which shows healthy tendons as homogeneous dark bands in all imaging protocols (Fig 4a), ultrasound is able to distinguish a fibrillar pattern running longitudinally through the tendon that correlates with collagenous fibre bundles (Fig 4b).

US findings of tendinosis include focal thickening with heterogeneous decreased echogenicity and loss of the normal fibrillar pattern (Fig 5a). Assessment of the area of abnormal texture with Colour Doppler US may show an area of increased blood flow (Fig 5b). Detection of these findings is not only useful for diagnosis of tendinosis but also for guiding treatments. Such treatments may include needling or fenestration, which induces haemorrhage and inflammation, both of which stimulate production of growth factors to promote healing. Platelet Rich Plasma (PRP) infiltration has the same effect. On the other hand, sclerotherapy - which is achieved by injecting a sclerosant such as polidocanol to occlude the vessels (Fig 6) - results in a decrease in inflammatory response. Although the latter is contradictory to other techniques mentioned earlier, which rely on an inflammatory response to induce healing, sclerotherapy has been shown to have positive results particularly in patellar tendinosis, lateral epicondylitis of the elbow and Achilles' tendinosis.

Continued overuse in the presence of tendinosis can result in progression to a partial or complete tear. Partial tears may be longitudinal or transverse. Longitudinal tears (also called longitudinal splits) course along the length of the tendon and may resemble tendinosis on US. Longitudinal tears are best seen when the tendon is imaged perpendicular to its course (along the short axis) (Fig 7). Transverse tendon tears are best seen when imaged parallel to the course of the tendon. Partial

thickness transverse tears may appear as an irregularity along one margin of the tendon or as a partial cleft within the tendon (Fig 8). A full thickness tear will present as a fluid-filled gap in the tendon with retraction of the proximal and distal segments (Fig 9). Dynamic US assessment during muscle contraction may improve visibility of a transverse tendon tear on ultrasound by opening the gap.

Tenosynovitis is an inflammatory reaction of the tendon synovial sheath, which is the most common type of overuse injury and is readily detected with US. It may present alone with pain located over the tendon and accentuated by tendon movements. Tenosynovitis may also present itself in association with tendinosis and tendon tears. US is highly accurate in detecting tenosynovitis (Fig 10) and in guiding treatment with injection of long acting steroids or PRP into the tendon sheath.

In summary, US has become the first line of management for acute soft tissue injuries. It provides immediate and accurate results in a safe and dynamic fashion. Tendon injuries are frequently better seen on US than with more complex imaging such as MRI. US also provides a means to deliver immediate and targeted treatment to decrease convalescence times.

Part II of this article will discuss imaging and treatment of ligamentous injury.

*(to be continued ...)*

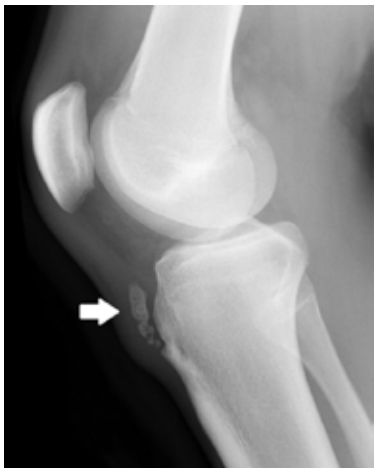

**Figure 1a.** Lateral X-ray of the knee showing the fragmented ossification centre (arrow) at the site of insertion of the patellar tendon into the tibial tuberosity as well as soft tissue swelling (Osgood-Schlatter's disease)

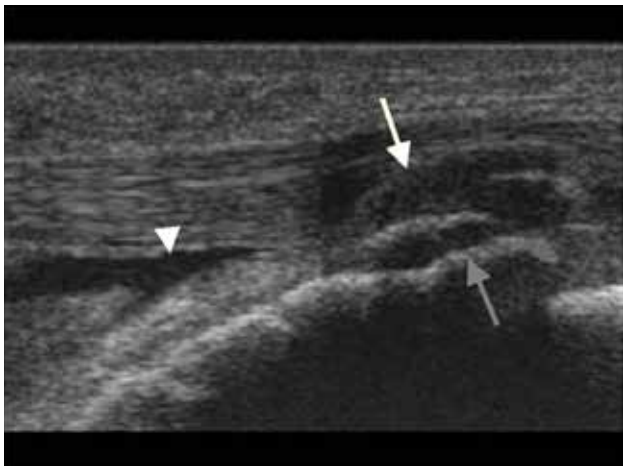

**Figure 1b.** Sagittal US image showing the fragmented ossification centre (grey arrow), soft tissue swelling over the ossification centre (white arrow) and fluid deep to the patellar tendon (arrowhead)

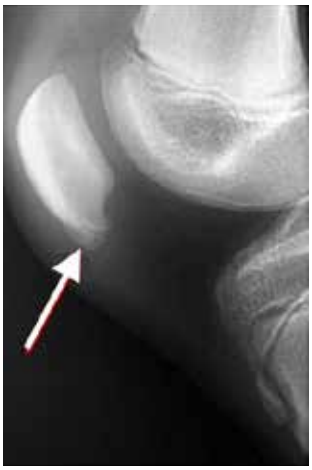

**Figure 2a.** Lateral X-ray of the knee showing a fragmented apophysis at the inferior margin of the patella (Sinding-Larsen-Johansson's syndrome)

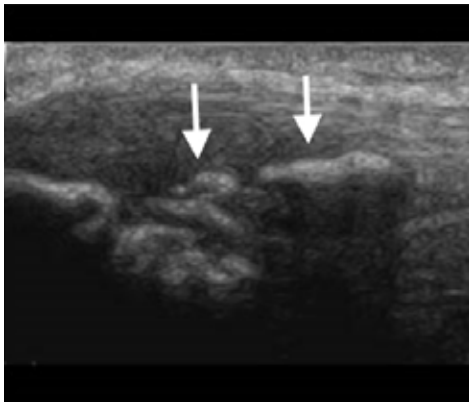

**Figure 2b.** Sagittal US image in a patient with Sinding-Larsen-Johansson's syndrome showing fragmented ossification at the insertion of the patellar tendon into the inferior pole of the patella

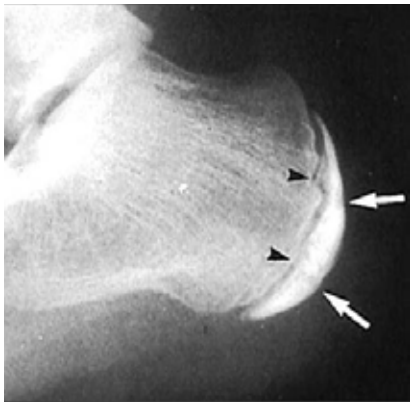

**Figure 3a.** This lateral X-ray of the calcaneus shows sclerosis of the posterior apophysis of the calcaneus (arrows) as well as widening of the epiphyseal plate (arrowheads), classic features of Sever's disease, an overuse injury at the insertion of the Achilles' tendon

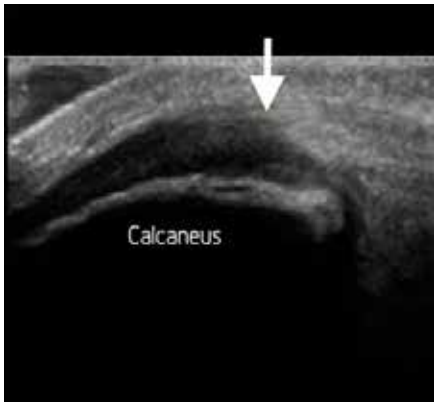


**Figure 3b.** Sagittal US image in a case of Sever's disease showing a fluid collection (arrow) at the insertion of the Achilles' tendon into the calcaneus

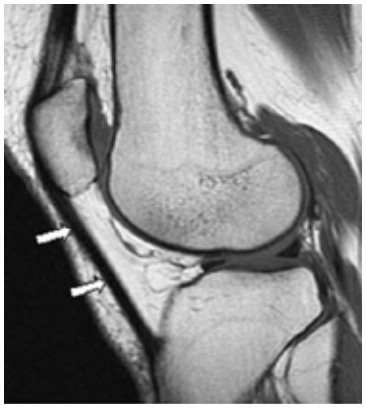

**Figure 4a.** Sagittal Proton Density-weighted MRI scan of the normal patellar tendon, which appears as a dark uniform band (arrows)

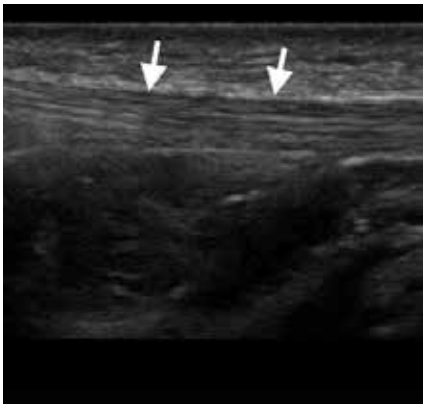

**Figure 4b.** Sagittal US of a normal patellar tendon showing a fibrillar internal structure (arrows) that correlates with collagen bundles running in a longitudinal direction parallel to the course of the tendon

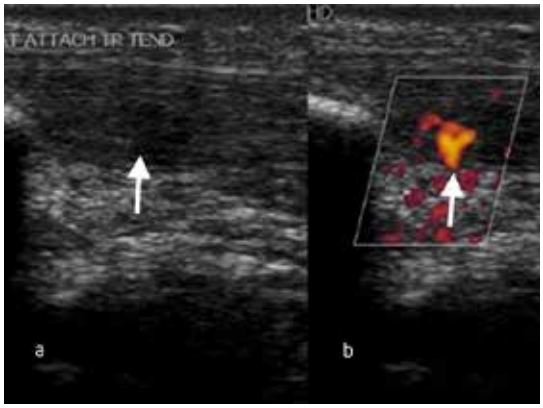


**Figure 5a and b.** Sagittal US scans through the proximal patellar tendon showing tendon thickening and loss of fibrillar pattern (a) with increased blood flow seen on Colour Doppler Imaging (b)

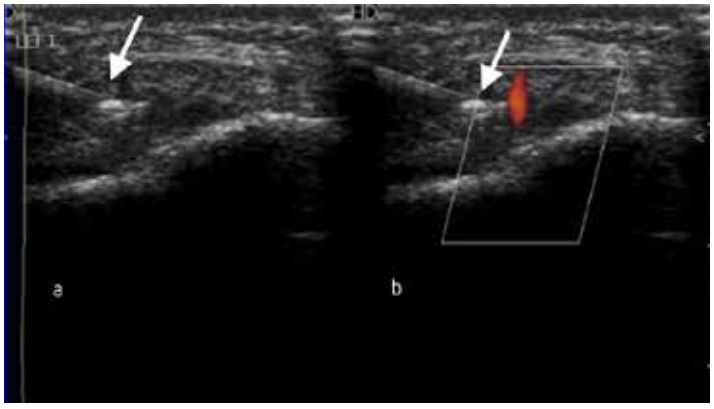


**Figure 6a and b.** Synchronised US scans in conventional (a) and Doppler (b) modes showing a guided sclerotherapy for patellar tendinosis

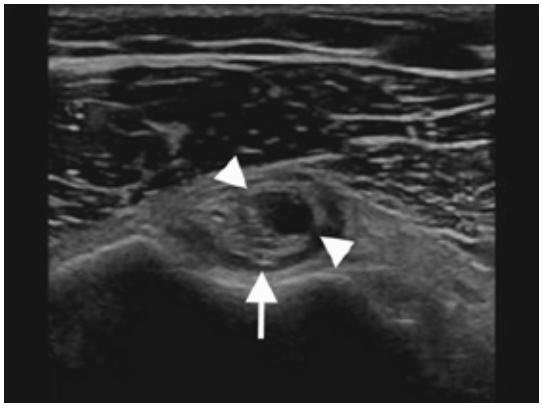

**Figure 7.** Transverse US scan of the long head of the biceps tendon (arrow) showing a split (arrowheads) within the tendon

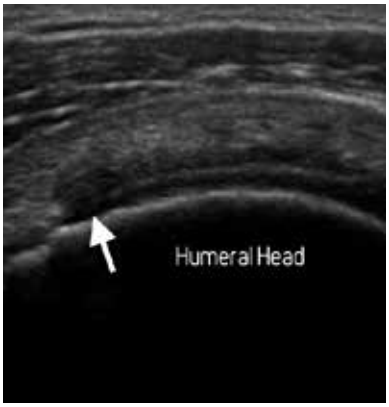


**Figure 8.** Longitudinal US scan of the supraspinatus tendon showing a partial cleft (arrow) on the deep aspect (articular side) of the tendon

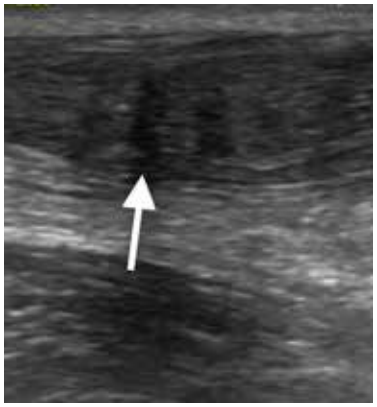

**Figure 9.** Longitudinal US scan of the Achilles' tendon showing a full thickness transverse tear (arrow)

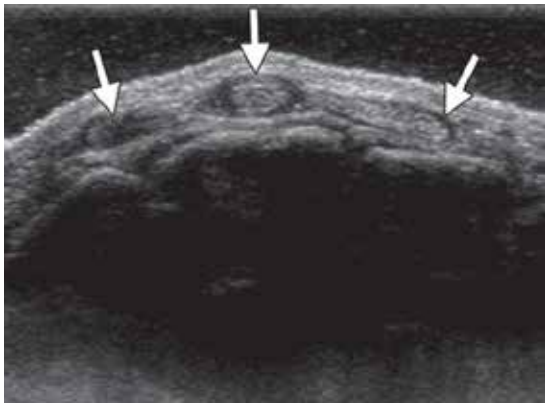

**Figure 10.** Transverse US scan through the extensor tendons of the index, middle and ring fingers at the level of the proximal metacarpal bones. Dark rings around each of the tendons (arrows) represent the thickened synovial sheaths

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