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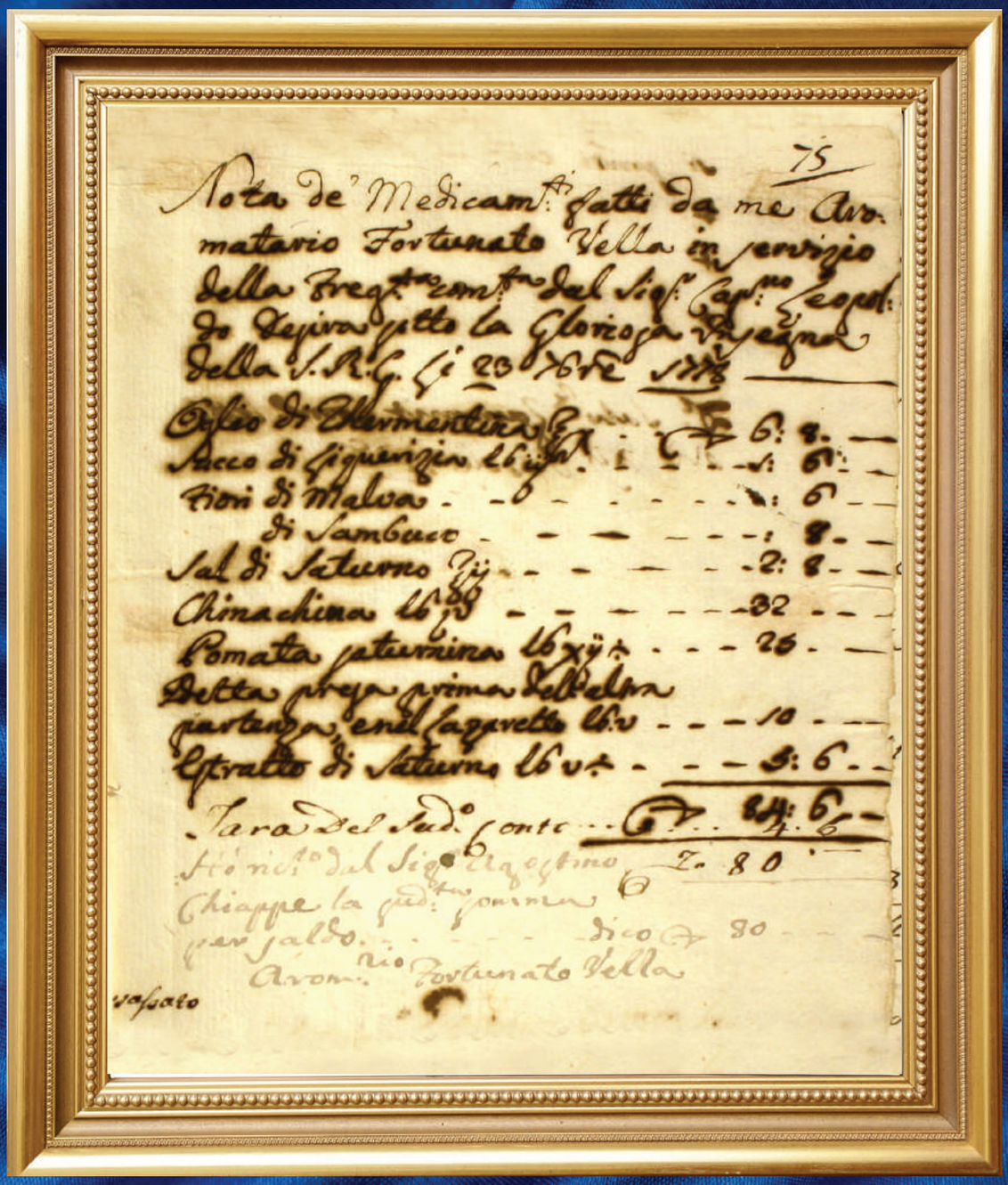
THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- Communication at the primary/ secondary care interface
- Meeting Prof. Albert Cilia-Vincenti
- Intermittent calf-muscle electrical stimulation on walking capacity

Volume 16, 2017 Issue 01 ISSN number 2313-8084



ACTIVATE THE HEART*

ACTIVATE LIFE[1,2]

GUIDELINE[1] CLASS I RECOMMENDED[1,4]

Change your symptomatic HFrEF patients to ENTRESTO®

- **Activates the heart's beneficial response** by enhancing the natriuretic peptide system, while maintaining RAAS inhibition[5,6]
- **20% reduced risk** of CV death or first heart failure hospitalisation vs enalapril ($P<0.0001$; ARR=4.7%)[5‡]
- **Significant improvements in Quality of Life** vs enalapril, as measured by reduced deterioration of heart failure symptoms and physical limitations ($P=0.001$)[7§]

When you see symptoms, IT'S TIME FOR ENTRESTO[5]

Entresto®
sacubitril/valsartan

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

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

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

‡ Primary end point.

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

ENTRESTO™ (sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥ 100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS). Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co-administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥ 100 mmHg. Patients with SBP < 100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP (< 112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR < 30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is > 5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is > 5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re-administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥ 1/10). Hyperkalaemia, hypotension, renal impairment. Common (≥ 1/100 to < 1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥ 1/1,000 to < 1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Frimley Business Park, Camberley, GU16 7SR, United Kingdom. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2016-MT-ENT-16-AUN-2016

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EDITORIAL

HEALTH PRIORITIES OF THE FIRST MALTESE PRESIDENCY OF THE EUROPEAN COUNCIL

The presidency of the European Council rotates among the EU member states every 6 months. During this 6-month period, the presidency chairs meetings at every level in the Council. Member states holding the presidency work together in groups of three, called 'trios'. This system was introduced by the Lisbon Treaty in 2009. The trio prepares a common agenda determining the topics and major issues that will be addressed by the Council over an 18-month period. Malta's stint concludes the current Trio of Presidencies, preceded by Netherlands and Slovakia.

This editorial will discuss two important health policies, relating to childhood obesity and cooperation between health systems.

CHILDHOOD OBESITY

In an interview with Euractiv, last December, Dr Chris Fearne estimated that 10% of the Maltese health budget is funnelled towards the management of the direct consequences of obesity. Dr Fearne also added that a remarkable 17% of preventable deaths in Malta is related to obesity. The full interview may be accessed at www.euractiv.com/section/health-consumers/interview/health-minister-drugs-pricing-will-top-maltas-eu-presidency/

There are numerous challenges in tackling childhood obesity, including the increasing production of processed food which is easily available and is relatively cheap. The use of processed food is also a social indicator of inequalities. A related challenge is food re-formulation with a view to decrease specific ingredients, including salt, sugar and saturated fats, and increase others, such as minerals and vitamins. Currently, there is much discussion on this topic at an EU level. In fact, the Commission has launched a White Paper on *A Strategy for Europe on Nutrition, Overweight and Obesity related health issues* [http://ec.europa.eu/health/nutrition_physical_activity/policy/strategy_en].

Interestingly, the *Health at a Glance: Europe 2016* [http://www.oecd.org/health/health-at-a-glance-europe-23056088.htm] reports that the average of self-reported overweight rates (including obesity) across EU countries increased between 2001-2 and 2013-14 from 11% to 18% in 15-year-olds. The largest increase during this period occurred in Malta where the rates now reach 30%. The Maltese Presidency is expected to present draft Council conclusions that will identify actions aimed at preventing the rise in childhood obesity. In this context, the Maltese Presidency also aims to develop guiding principles on the procurement of food in schools. The aim is to shift procurement rules from focusing on the cheapest price to the cheapest *& healthiest* offers.

COOPERATION BETWEEN HEALTH SYSTEMS

Europe has long aspired to promote the free movement of citizens by facilitating the transfer of health records across different member states. Such cooperation between health systems is included in *Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.* In this respect, the Maltese Presidency will focus on enhancing cross-border cooperation. This is envisaged to also include the establishment of centres of excellence, for example in the area of rare diseases.

Another theme is the accessibility and affordability of medicines, with a focus on transparency in the way pharmaceutical companies negotiate with the purchasing authorities. Currently, individual member states are strongly discouraged from sharing the prices they get among themselves, thus fuelling the prices of medicines. The Maltese presidency will spearhead the setting-up of joint regional procurement mechanisms according to countries' GDP. The will follow on the steps of the Benelux countries which have already started such an initiative.

The third theme concerns cross-border training for doctors. The Maltese presidency aims to launch a structured, Erasmus-like post-graduate training for doctors, which is currently non-existent. This March, during the Maltese Presidency, the Commission will launch the European Reference Networks [ERNs], which are possibly a step towards this direction.

Logically, numerous meetings are being held in Malta during these 6 months, including *Childhood Obesity: halting the rise* [23-24 February], a technical workshop on collaborative procurement strategies, structured cooperation, rare diseases and ERNs [1-2 March], a Ministerial Conference on Developing Medicines for Rare Diseases [21 March] and the *eHealth week* [9-12 May].

Ian Ellul

Cover: In the 18th century, corsair ships were only allowed to leave the Maltese harbour if they had a doctor on board. This doctor was responsible for the provision of the medicine box on board the ship. In fact, one finds this particular condition specifically written in every enrolment agreement. A medicine box used on board a frigate commanded by Captain Leopoldo Desira in 1778 included the following items:
'Oglio di Thermentina' - Turpentine oil
'Succo di Liquerizia' - Liquorish roots
'Fiori di Malva' - Malva/Mallow Flowers
'Fiori di Sambuca' - Elderberry Flowers
'Sal di Saturno' - Type of Mercury
'Chinachina' - Citrus Myrtifolia
'Pomata Saturina' - Type of Mercury
'Estrato di Saturno' - Type of Mercury

Photo Credit: Liam Gauci, Curator, Malta Maritime Museum

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

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

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GMMS GERMAN-MALTESE MEDICAL SOCIETY
MMSA
MPSA
MADS Malta Association of Dental Students

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

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

FLAME STUDY RESULTS[1]

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

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

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

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

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

Ultibro Breezhaler inhalation powder, hard capsules

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

PRESENTATION: Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. **Method of administration** For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. ***Asthma:*** Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol or glycopyrronium. Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. *Paradoxical bronchospasm:* As with other inhalation therapy, administration of Ultibro Breezhaler may result in paradoxical bronchospasm which can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. Narrow-angle glaucoma: No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. Urinary retention: No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2 adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2 adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of beta2 adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention,, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, , gastroenteritis tachycardia, palpitations, , insomnia Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003 , EU/1/13/862/007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872

2016-MT-ULT-10-NOV-2016

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2. Novartis Europharm Ltd. Ultibro Breezhaler Summary of product characteristics.

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AUTHORS

Dr Jason Attard MD
is a specialist trainee in public health medicine and a visiting assistant lecturer with the Department of Pathology. His main interests are health statistics, epidemiology and cancer research. The co-authors of the article are Drs Charmaine Gauci & Julian Mamo.

Dr Alfred Gatt B.Sc.(Hons.) M.Sc.(Pod.) PhD SRPod
is a lecturer at the Podiatry Department, Faculty of Health Sciences. Special interests include Clinical Biomechanics, 3D motion capture, Diabetic Foot Biomechanics and Gait Analysis. He is co-ordinator of the MSc in Clinical Biomechanics offered by the UOM.

Christian Ellul B.Sc.(Hons.) M.Sc. SRPod
conducted various research on peripheral artery disease in high risk populations. He was also involved in a government project relating to the innovative use of thermography as a prospective diagnostic tool for diabetic foot complications.

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

ISSUE GUIDE

TheSynapse

COMMUNICATION AT THE PRIMARY / SECONDARY CARE INTERFACE

A REVIEW OF THE LITERATURE AND A STAKEHOLDER ANALYSIS

JASON ATTARD, CHARMAINE GAUCI & JULIAN MAMO

ABSTRACT

INTRODUCTION

Information linkage between primary healthcare providers and secondary care providers in Mater Dei Hospital has traditionally been poor in Malta. The ticket of referral and the discharge letter have traditionally been the only way continuation of care is communicated via the two sets of providers and these have been criticized in terms of content, completion or for their absence on many occasions. The aim of this study was to assess the current changing situation and recommend measures that could be taken to improve matters in the foreseeable future.

METHODOLOGY

A qualitative methodological approach was conducted during March-April 2016. Semi-structured interviews were performed on five key personnel across the primary-secondary care interface. Respondents were asked on their views on the current referral process, the current discharge process, and primary/secondary care collaboration for the management of chronic diseases. Subsequent questions explored the possible negative aspects for each interface point and what measures could be used to improve them.

CONCLUSION

A multi-faceted problem requires a multi-faceted approach encompassing changes in the current business process, improvements in communication at the referral and discharge stages, and having robust information technology support.

INTRODUCTION

Modern healthcare systems are complex organisations through which patients must navigate to access care. Coordination of care across the primary/secondary care interface via good communication is essential in the delivery of good quality healthcare.

According to the European Working Party on Quality in Family Practice (EQuiP), improving the quality of cooperation is not considered a high priority in any of the European healthcare systems.[1] However, problems at the primary/secondary care interface result in poor quality care. As each component of care focuses primarily on its own affairs, patients are 'left in limbo' with no party taking ownership of the patients' overall progression. This undercuts communication through the healthcare system.[1]

Continuity of care is the extent in which the patient journeys along a series of separate healthcare events in a coherent and seamless way despite involvement of different healthcare professionals across different levels of care.[2]

There are two main types of continuity of care:

1. Relational continuity,
2. Managerial continuity.

Relational continuity refers to the sustained relationship between one or more practitioners and a patient spanning across individual healthcare episodes.[3]

Managerial continuity refers to the degree in which complex and specialised healthcare is delivered in a coherent, consistent and integrated way. Informational continuity is an important tool for management continuity and refers to the appropriate transfer and use of patient information to link individual healthcare episodes.[3]

The focus of this report is mainly on informational continuity.

In Malta, there are two main pathways to specialist services: public and private. General practitioners (GPs) in both the public and private sector act as gatekeepers. They can refer patients to either public or private specialists. However, patients have direct access to both GPs and specialists in the private sector. Patients can be referred by GPs to public specialists either using a paper-based or electronic format. Following discharge from public hospitals, patients are provided with an Electronic Case Summary (ECS) which is generally written by Foundation Year (junior) doctors. The ECS, together with medicines data, laboratory and imaging results, and hospital appointment data are available to patient-nominated GPs via the web-based myHealth system.

There are a number of different models of interaction across primary and secondary care,[4] however, there are two main points which are common to all where clinical handover occurs:

1. The Referral: from primary care to secondary care,
2. The Discharge: from secondary care to primary care.

The referral letter is the predominant means of communication from GPs to specialists in secondary care.

Continuity of care requires good communication between the GPs and the specialist. Informational continuity can only be achieved when the transfer of information occurs in a clear and complete manner.

In Malta, Chetcuti et al. and Cassar et al. showed that only two thirds of all referral letters are completely legible with about one third being partly legible. In these two studies, almost all tickets of referral were hand written.[5,6]

Correct patient details are essential to ensure basic continuity of care. Chetcuti et al. and Cassar et al. showed that only the patients' name and surname were consistently written down in the referral letter. The unique national identification number, which is used to book appointments and link data, was missing in 9% and 0.6% of cases respectively.[5,6]

Cassar et al. found that the doctor could not be identified in 5.4% of cases whilst Chetcuti et al. showed that the referring doctor's name was missing in more than 20% of cases.[5-6] Chetcuti et al. suggested that the fact that a significant proportion of GPs failed to provide clear contact details implies that they do not expect or are not interested in receiving feedback from secondary care.[5]

Clinical details in referral letters were found to be consistently poor across many studies.[5-9] Westerman et al. noted that only 39.5% of all referral letters were of good to excellent quality. Other studies showed that relevant clinical information was missing in 5.4% and up to 85% of cases;[5,10] between 22.8% and 25.1% of referrals did not include primary care-based investigations in the referral letter.[6,10]

Inappropriate referrals cause inequity to specialist services and inefficient use of limited healthcare resources.[11-12] In one study, 13% of referrals were deemed as inappropriate with a significantly higher proportion of referrals to medical specialities (19.6%) rather than surgical specialities (8.6%) ($p = <0.01$).[10] Cassar et al. found that up to 44.2% of all surgical referrals were found to be inappropriate, with the majority being referred to the wrong surgical subspecialty.[6]

Reasons for referral from primary care to secondary care vary and are not simply to establish a diagnosis, for specific investigations or for treatment or an operation. Other reasons for patient referral include patient reassurance, reducing medico-legal risk, handing over of care or to obtain a second opinion.[13] Also, perceived patient pressure is a strong independent predictor to refer patients to secondary care.[14]

The discharge process involves a transfer of responsibility from specialists in secondary care to GPs in the community.[15] The discharge letter or summary is the traditional tool used to communicate the clinical information required for seamless continuity of care. The provision of a timely, complete and accurate discharge summary to GPs can prevent adverse events, and hospital readmissions.[16-17]

The availability of the discharge summary is not only dependent on its prompt completion but also on its successful transfer to primary care. In a systematic review, Kattel et al. showed that medians of 55% and 85% of discharge summaries are transferred to GPs within the first 48 hours and four weeks, respectively. This was despite the fact that the discharge summaries were almost always available (98%) in the patient's record.[18]

Kattel et al. also showed that administrative data such as patient demographics and admission/discharge dates were almost always included in the discharge summaries (both medians of 97%). However, other administrative data, namely the physician's name and GPs name were less often included (81% and 70%, respectively). The primary diagnosis and the hospital course were almost always provided (median of 99%). However, other diagnoses (median of 82%), diagnostic results (median of 60%) and discharge medication (median of 78%) were less consistent. Discharge instructions and follow-up plans were included in medians of 98% and 42% of discharge summaries respectively. Whilst all of these indicators improved when compared to a previous systematic review,[19] pending tests at discharge fell from 60% to a median of 25%.

The accuracy of information within a discharge summary is a very important component of continuity of care. Wilson et al. found that just over one third of discharge summaries contain errors of which 17.5% were medication errors, 17.3% were clinical errors and 14.4% were follow up errors.[20] Also, McMillan et al. noted that the number of discharge letters with one or more errors was significantly greater in medical patients when compared to surgical patients. This is probably due to the fact that medical patients were older, often taking a greater number medicines and were more likely to have had changes in their medication during the inpatient stay. Whilst error rates were high, the majority (87.4%) were minor.[21]

Completeness of information is another important component of continuity of care. It is essential that the discharge summary includes a full list of drugs that the patient is expected to take irrespective of the nature of admission to hospital, so as to avoid the possible assumption that a medicine was discontinued.[22] Also, it is crucial to state when and why a drug has been discontinued.[21] The same is true for adverse drug reactions in hospital. Green et al. noted that up 89% of adverse drug reactions were not recorded in the discharge summary.[23]

To the best of the researchers' knowledge, there have been no studies to date which investigated the current patient care hand-over across the primary-secondary care interface in Malta. The aim of this study was to investigate the weak links within the communication at the primary-secondary care interface and to identify measures that could be taken to improve matters in the foreseeable future.

METHODOLOGY

In this observational and descriptive type of research, five stakeholders across the primary and secondary care interface were identified. These were contacted in writing, all of whom accepted to be interviewed. The respondents consisted of one senior general practitioner (more than 10 years of clinical experience) (R1), one junior general practitioner (less than 10 years of clinical

experience) (R2), one consultant in a surgical speciality (R3), one consultant in a medical speciality (R4) and one public health physician (R5). Fieldwork took place in March and April 2016. After obtaining informed written consent, respondents were asked semi-structured questions on their views on the current referral process, the current discharge process, and primary/secondary care collaboration for the management of chronic diseases. Subsequent questions explored the possible and negative aspects for each interface point and what measures could be used to improve them (Table 1). Interviews were audio-recorded and analysed for common themes.

RESULTS AND DISCUSSION

Three main overarching themes emerged from the interviews: the business process, communication, and information technology support.

1. THE BUSINESS PROCESS

The researchers identified a number of changes that could improve the business process across the primary/secondary care interface.

Referral guidelines and policies

Referral guidelines and management proformas "are essential" (R1). According to the results of a Cochrane review, the dissemination of structured referral guidelines coupled with regular follow-up can be used for common conditions.[11] However, passive distribution of such referral guidelines do not improve the quality of referral letters.

A recent study by Wahlberg et al. showed that paper-based and electronic referral templates with regular follow-up on their use improved the quality of the referral letters for dyspepsia, suspected colonic malignancy and chest pain.[24] Referral guidelines and management proformas need to "be based on objective scientific evidence" (R5) and could include "investigations (which could) be ordered beforehand to speed up the process" (R2), so that patients can be investigated appropriately prior to referral. This allows for better prioritisation of appointments based on urgency, for example fast-track colon cancer referral to the surgical department (R3).

The main limitation of using referral templates is that they should only be used for common conditions as there is the risk that they become more of a burden than of help. Akbari et al. suggested that this might be addressed by advances in health informatics.[11]

There is a "need for leaders in primary care to guide primary care providers to what is good practice in referrals" (R5). Whilst R5 stated that "primary care providers need to be able to classify the seriousness of the case", R4 stated that "an urgent referral should be accompanied with a phone call". R4 continues that

Referral Process	
Q1	What do you think about the current referral process?
Q2	What are the positive aspects of the process?
Q3	What are the negative aspects of the process?
Q4	What measures do you think could improve the process?
	Prompts: easy access to specialists/referral guidelines/management proformas/training of GPs/GP phone link to a referral centre/easier electronic referral forms
Discharge Process	
Q5	What do think of the current discharge process?
Q6	What are the positive aspects of the process?
Q7	What are the negative aspects of the process?
Q8	What measures do you think could improve the process?
	Prompts: eliminate hand written discharge letters/provide discharge letters on the same day/training of juniors doctors/decrease work load/standardisation of discharge letters
Q9	Do you believe that the current discharge process provides complete, accurate and relevant information for continuity of care?
Primary/Secondary Care Collaboration for the Management of Chronic Diseases	
Q10	What do you think about primary/secondary care collaboration during management of chronic diseases e.g. COPD, cancer etc?
Q11	What barriers do you think there are for such collaboration?
Q12	What measures do you think could improve the collaboration?
	Prompts: standardised email consultation process/protected time for specialists to answer emails/collocation of GP and specialist/GPs in specialist centres and specialists in primary healthcare
Q13	Would you like to add anything that has not been mentioned in this interview and you think will help to improve communication at the primary/secondary care interface and in so doing the continuity of care of patients?

Table 1. Semi-structured interview questions.

"referrals should not have 'urgent' written on the referral form as per policy ... and that ... inappropriate referral forms should be turned down". However, R5 argues that "this 'punishes' the patient and that the real long-term solution... is to make sure that electronic patient records are implemented at both ends, both at the primary care end and secondary care end and integrated so that they can communicate easily from one system to the other".

Patient registration

As R5 explained, "it is not easy to identify the patients' family doctor." Patient registration, where patients have a named GP, could enhance relational "continuity of care" (R2). This is a formal way to "build a relationship between the patient and GP ... you would expect the quality of the referral letter to be better when the GP knows the patient better ... and the discharge letter will be sent to him" (R3). This initiative is also supported in the literature.[3,25]

Shift to primary care

GPs should be allowed to "have more responsibility and have patients 'discharged' from outpatients to their care especially with optimised treatment" (R2). Also, "evidence-based care pathways for named diseases" can help GPs actively follow up patients (R4). As one participant explained, "handover ... of breast cancer care five years after diagnosis to a group of private GPs has only just started" (R3). This shared care approach based on a chronic condition is supported by the literature.[25]

Quid pro quo

R4 suggested that private GPs should "give something back" for hospital services. For example, in order to able to order a prostate specific antigen (PSA) blood test, private GPs must include examination findings and come to a yearly one hour course on prostate management. "Organising seminars on particular topics (can be used as a platform to get to) know each other better" (R3). Indeed, R1 clearly stated that "I work best with people I know."

2. COMMUNICATION

Respondents felt that communication across the primary/secondary care interface could be improved. Respondent R2 felt that during the discharge process it is important to liaise "with the patients' GP with regards to the social aspect before the patient is discharged, especially for elderly and complex medical cases" (R2). Respondent R1 commented that "a notification when a patient (of ours) is discharged from hospital is the way forward".

Standardisation of discharge summaries improves access to information, better describes the hospital episode, and ensures informational continuity of care.[26] The ECS is generally written by the "youngest member of the team" (R3) and whilst "lately, there has been quite an improvement" (R1) "the quality ... needs to improve" (R3). "Treatment on discharge is not always written ... and treatment ... which was stopped (and the reason why) is not always mentioned in the discharge note" (R2). One possible solution is having the consultant or resident specialist review the ECS before it is sent out (R3, R4). Medicine reconciliation could be improved by having a single shared electronic patient record between primary and secondary care providers and the community pharmacist.[27] Also, there is a need for continuous professional development (CPD) "emphasising the importance of proper record keeping ... explaining the need ... of accurate input, the importance of structuring of data and the importance of timeliness" (R5). The accuracy of discharge summaries might be improved with training and education of junior doctors.[21,28-29]

Two other modes of communication across the primary/secondary care interface are emails and phone calls. "Email is a good way of communicating because it is more instant than letters and it allows you some time to reply which is better than a phone call ... The problem is the overload... that sometimes the effort you put in to answering your emails takes up a lot of time" (R3). However, whilst "emails are useful ... a phone call is better" (R1) "for urgent communication" (R4).

THE myHealth SYSTEM IS "SO CUMBERSOME"

GPs "NEED BETTER ACCESS" TO THEIR PATIENTS' DATA

3. INFORMATION TECHNOLOGY SUPPORT

Information Access

GPs "need better access" to their patients' data (R1). The myHealth system is "so cumbersome ... it should be easier to use" (R4). Often the "most needy patients cannot make use of the system" (R1). Also, specialists in secondary care have no way to check the ECSs or blood results of their patients from home (R4).

Electronic referral form

Respondents commented that the online referral form is "convenient"; however "it isn't very friendly and quite slow on the mobile phone" (R2). Whilst it serves as a "bridge between the paper referral and the telephone call ... the uptake has been poor" (R3). Basic patient and doctor data, legibility and clinical information can be improved upon by introducing electronic standardised proformas. These proformas would automatically populate administrative data from electronic health records and provide a logical framework for referral depending on the speciality of interest. In one study, the amount of clinical information handed over improved from 18.9% to 56% after the introduction of a standardised electronic means of communication.[30] This also led to an improvement in the prioritisation of appointments. However, another study showed that the introduction of electronic referral letters on top of providing good-quality written feedback did not appear to improve the quality of the referral letters.[31]

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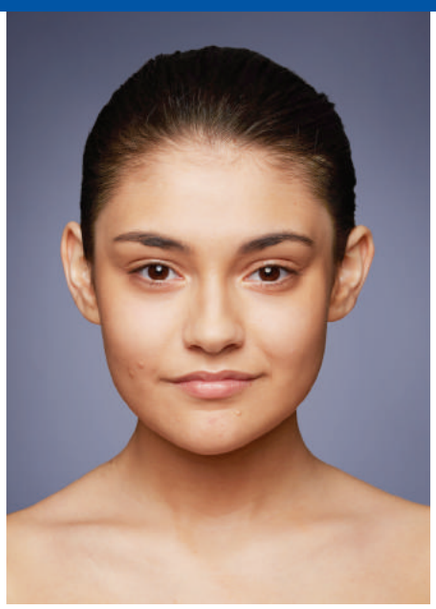

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- Treats comedones[2] and inflammatory lesions[5]
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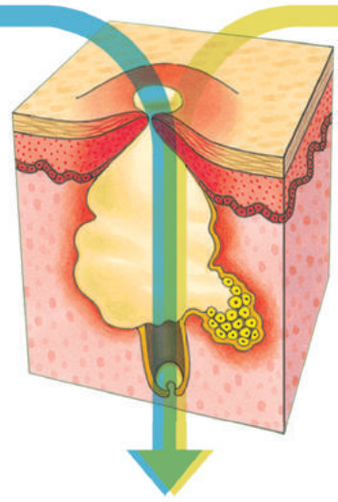
- Anti-inflammatory action[5]



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Reduces inflammation
Kills bacteria
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- **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]

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- Using Duac less often, or stopping for one or two days before starting again

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

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

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Electronic discharge summary

Discharge summaries should be ready on the same day of discharge from hospital and either sent to the patients' family doctor by email or given directly to the patient.[32-33] A systematic review showed that electronic discharge summaries improve timeliness in relation to paper discharge letters, and also, ensure completeness and accuracy of clinical information.[34] They also ensure legibility.[32] However, electronic discharge summaries have a higher number of errors and/or omissions including medicine transcription errors to paper discharge letters.[28,35]

Since the introduction of the ECS, the discharge letter is "more structured", with reliable demographic information and "prompts" to complete the form (R5). However, according to one respondent, it is a "glorified word document with some drop down menus" and "more drop down menus especially for the discharge diagnoses are needed" (R4). Another respondent stated "the discharge letter should be produced automatically and electronically from the case notes... (however, introducing electronic health records) is very very difficult and I feel that the IT system in our hospital is not very strong" (R3).

CONCLUSION

Information linkage between primary healthcare providers and secondary care providers in Mater Dei Hospital has traditionally been poor in Malta. The ticket of referral and the discharge letter have traditionally been the only way continuation of care is communicated via the two sets of providers and these have been criticized in terms of content, completion or for their absence on many occasions. This study suggests that improving communication at the primary and secondary care interface requires a multi-faceted approach through improvements in the business process, communication and information technology support.

The main limitation of this study lies in the small number of potentially biased respondents. A follow up study recruiting more participants across the primary and secondary care is recommended.

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SEROXAT ABRIDGED PRESCRIBING INFORMATION

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

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

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

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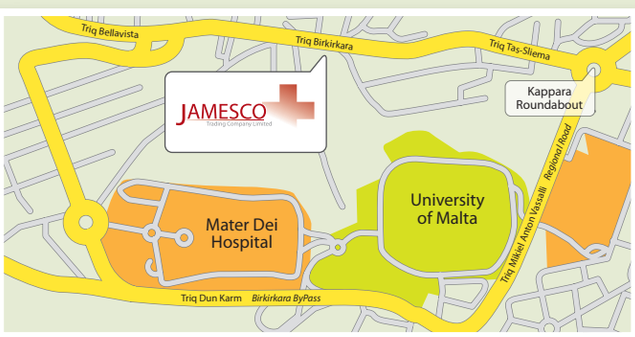

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INTERMITTENT CALF-MUSCLE ELECTRICAL STIMULATION ON WALKING CAPACITY

IN PATIENTS LIVING WITH TYPE 2 DIABETES MELLITUS AND INTERMITTENT CLAUDICATION

CHRISTIAN ELLUL
ALFRED GATT

ABSTRACT

A prospective, one-group, pretest-posttest study design was employed on forty participants (n=40) with bilateral limb ischemia (ABPI <0.90), diabetes mellitus and calf muscle claudication. Participants received a fixed program of calf muscle electrical stimulation with varying frequency (1-250Hz) on both ischemic limbs (N=80) for 1 hour per day for 13 weeks. The absolute claudication distance was employed as serial outcome measure to assess maximal walking capacity at baseline and following the intervention. Statistical significant improvement was registered in mean absolute claudication distance (p= 0.000; Wilcoxon Signed Ranks test) at follow-up relative to baseline.

INTRODUCTION

Peripheral artery disease (PAD) is a highly prevalent disease estimated to affect over 200 million people worldwide.[1] It is defined as a partial or complete obstruction of arteries due to the development of atherosclerosis[2] and can affect all arteries distal to the aortic bifurcation.[3] The presence of lower-limb atherosclerosis significantly increases the risk of cardiovascular and non-cardiovascular-related death while the disease causes walking impairment that can lead to intermittent claudication.[4] Patients with concomitant diabetes mellitus are considered particularly vulnerable as they carry a poorer prognosis than those with either disease alone.[5,6]

Evidence shows that claudicants have poorer abilities in daily tasks such as ambulation,[7] reduced quality of life[8] and have been associated with higher prevalence of depression.[9] Furthermore, several studies have shown that poor walking time is an independent predictor of cardiovascular events and mortality in PAD patients.[10,11]

Guidelines on the management of patients with PAD recommend supervised exercise training as a first line therapy to improve claudication symptoms.[12,13] Exercise training comes with a number of barriers particularly in the elderly population. The majority of studies advocate supervised exercise programs; however, the usefulness of unsupervised programs has not been well established.[12] Factors such as motivation to exercise, osteoarthritis and psychosocial factors may preclude adherence to any form of exercise therapy.[14,15] Patients with co-morbid disease such as congestive heart failure or chronic obstructive pulmonary disease may also be advised to avoid strenuous cardiovascular activities.

As a result, in this vulnerable population there is a clear lack of treatment options available. In this context, electrical stimulation (ES) technology has been proposed as a potential alternative or adjunct to traditional exercise.[16-19] However, only a few studies have evaluated the effectiveness of this therapeutic measure in PAD patients.[18-20] Such studies are either conducted on laboratory ischemic animal models while those actually conducted on human are few and far between.[19-20] This paucity has contributed to uncertainty amongst health care professionals on the use of such a technology as part of a treatment plan.

The aim of this study was to provide further insights on electrical stimulation by investigating whether sustained calf-muscle electro-stimulation for a duration of 13 weeks results in measurable improvement in functional walking capacity in PAD patients having concomitant diabetes mellitus and claudication symptoms.

METHODOLOGY

Participants were recruited randomly from a Mater Dei hospital vascular database of patients with the following inclusion criteria:

1. Diabetes;
2. PAD defined with an Ankle Brachial Pressure Index (ABPI) <0.9;
3. Abnormal spectral waveforms on the dorsalis pedis and posterior tibial arteries on both legs and suffering from calf muscle intermittent claudication reproducible on a graded treadmill test.

Exclusion criteria were aimed to control confounding variables. These included patients with renal disease, medial artery calcification (ABPI >1.3) and sensory or autonomic neuropathy. Patients on oral claudication therapy or who had impediments to treadmill exercise, including previous foot/ toe amputations and physical/physiological reasons such as blindness, were also excluded.

Eligible subjects were initially assessed (pretest) to establish a baseline and followed up after 13 weeks of ES intervention (posttest) in a temperature and humidity controlled laboratory at the Faculty of Health Sciences, University of Malta. The resting ABPI and spectral Doppler waveforms of the posterior and dorsalis pedis artery were measured at baseline to confirm the presence of PAD in accordance with the inclusion criteria set in the study.

The absolute claudication distance (ACD) was employed as the primary outcome measure to evaluate the therapeutic effects of ES on claudication symptoms. The ACD is defined as the distance at which claudication becomes severe and forces the participant to stop[21] and was acquired using a graded treadmill protocol.[22-23] The treadmill was initiated and maintained at a fixed speed of 3.2km/h while the treadmill grade was gradually increased by 2 degrees every 2 minutes up to a maximum of 10 degrees from an initial inclination of 0 degrees in accordance with the literature.[24]

The *Veinoplus Arterial* model 2.1 (Ad Rem® Technologies, France) was used to generate the muscular contractions throughout the course of the intervention as per manufacturer's instructions. This battery-operated device consists of a central unit with two adhesive electrodes attached transcutaneously on the calf muscle, generating the required electrical stimulation at varying frequencies (1-250Hz) through a series of rectangular pulses of low energy (<25uC) and low voltage (50V peak) within a fixed 1 hour session.

Following a demonstration session, recruited participants were given written instructions and log sheets to record daily use. Participants were instructed to use the device at any time of the day for 13 consecutive weeks in the seated position with the legs hanging down, manually and gradually increasing the intensity of the stimulation from the control unit along the intervention period. The optimal intensity of stimulation was set manually at the beginning of each session by the participants and was defined as the point at which a visible but comfortable calf contraction occurred on both limbs.

At the end of the 13 week period, participants were re-assessed under the same baseline laboratory conditions and utilizing the same treadmill protocol. Data was analyzed on IBM SPSS version 21. The Kolmogorov-Smirnov test revealed a non-normal distribution of the ACD data sets for both baseline and follow-up results. As a result, the Wilcoxon Signed Rank Test was used to evaluate for any significant differences in mean absolute claudication distance (ACD) at follow-up relative to baseline. Ethical permission was sought and obtained from the University Research Ethics Committee prior to initiation of a prospective, one-group, pretest-posttest study design. All participants signed an informed consent prior to inclusion in the study after being provided with an information sheet in Maltese or English, depending on their preferred language. All investigations were carried out in accordance with the Declaration of Helsinki (2008).

RESULTS

From an initial assessment of 81 subjects, forty participants (30 males, 10 females; N=80 limbs) satisfied the inclusion criteria and were recruited in this study. At baseline, the cohort had a mean age 71 years (SD= 7); mean BMI 28.8 (SD= 3.7) and mean ABPI 0.70 (SD= 0.12).

The mean intervention period was 91.68 days (SD= 6.23) as quantified from the participant's log-sheets. No evidence of non-compliance was reported while no subjects were lost to follow-up.

At baseline, the mean ACD registered was 333.71 meters (SD= 208). After 13 weeks of treatment the mean ACD was registered to be 470.7 meters (SD= 279). This translated in a mean improvement in the ACD of 137 meters (SD= 136), an improvement in maximum walking capacity of 41% relative to baseline that was found to be statistically significant (p= 0.000; Wilcoxon Signed Ranks Test).

DISCUSSION

This study confirmed a significant improvement in maximal walking capacity on a treadmill in claudicants as evidenced by a mean increase (p=0.000) in the ACD of 137 meters following a consecutive period of 91.68 days (SD= 6.23) of 1 hour ES of the calf muscles per day.

The effects of ES on ischemic muscles is thought to include the augmentation of angiogenesis and morphological muscular adaptation.[25-27] Studies have shown that ES augments the endogenous production of growth factors including vascular endothelial growth factor (VEGF) and expression of VEGF receptors such as fetal liver kinase 1 (FLK1), facilitating angiogenesis in ischemic muscle.[25,28,29] The growth of new capillary networks within the ischemic muscle increases blood flow and oxygen availability to the exercising muscle, thereby lessening the ischemic symptoms.[26] Additionally, muscle fiber activation is enhanced by ES, while selective recruitment of fatigue-resistant Type 1 muscle fibers is also thought to contribute to the improvement in claudication symptoms.[26,27] These findings open up new opportunities of non-invasive treatment options for the claudicants population. Electrical stimulation has the potential of improving the functional walking capacity in claudicants with diabetes, thereby improving their outlook and quality of life. Furthermore, the ability of ES to produce muscular exercise activity without gross movement of joints or whole body exercise is an added advantage particularly in patients with co-morbid disease such as severe osteoarthritis, chronic heart failure or pulmonary diseases.

Thus, ES should be considered as an adjunct treatment modality in order to improve walking capacity in symptomatic PAD patients living with Type 2 diabetes, particularly those who are impeded from undergoing vascular procedures, have already undergone these procedures but remain symptomatic and those who cannot perform exercise due to co-morbid disease.

It is recommended that a randomized controlled trial in a larger population is conducted in Malta with a view to strengthen the findings. This was not possible during this study due to ethical considerations regarding the use of placebo-controlled randomized trials and the inability to recruit an appropriately matched control group as a result of a limited number of available participants satisfying the inclusion-exclusion criteria. By evaluating the macro- and micro-circulatory response to ES, future studies may also reveal whether the effectiveness of ES of varying low to high frequencies may extend beyond improving muscular ischemic symptoms.

CONCLUSIONS

Electrical calf muscle stimulation significantly increased walking capacity in claudicants living with type 2 diabetes. ES should be considered as an adjunct treatment modality for claudicants who are precluded from following active physical exercise programs, such as the elderly, those with a lack of motivation to exercise, patients with arthritis and other physiological and psychosocial factors that make walking difficult.

FUNDING

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Dr Albert Cilia Vincenti with his wife Grace, having recently moved into their house in Winchester – autumn colours of 1981

IT'S NOT JUST ABOUT THE CORPSES

Semi-retired pathologist Professor Albert Cilia-Vincenti speaks to *The Synapse* about his work, his experience and the changes he has witnessed in pathology over time.

TS: WHERE DID YOU TRAIN AND WORK?

I qualified in medicine in Malta in 1969 and in 1971 moved to London where I trained almost exclusively in histopathology (or surgical pathology, as the Americans call it) for 9 years at The Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals. At Charing Cross and The Middlesex, I was also a London University lecturer and one of HM Coroner's pathologists in Central London. I was appointed Consultant Histopathologist to The Royal Hampshire County Hospital in Winchester in 1980, where I was eventually made Pathology Services Director to Winchester & Eastleigh Health Care Trust.

With histopathology senior registrar Ken Jarvis [right], Royal Marsden, London. Christmas drinks 1971 - Dr Cilia Vincenti's first year in London.

The Winchester Coroner and the Hampshire Constabulary wanted me to be appointed Home Office Pathologist for Hampshire, but this involved only forensic work in which I was not interested. After 15 years in Winchester I returned to Malta as Senior Lecturer and consultant pathologist and retired when I was Chairman of Pathology Services and Associate Professor. I presently work as a diagnostic surgical pathologist in private practice.

TS: CAN YOU COMMENT ABOUT THE VAST CHANGES YOU HAVE WITNESSED IN THE FIELD OF PATHOLOGY OVER THE COURSE OF YOUR CAREER?

From one subject of clinical pathology, pathology has, in 50 years, grown into so many sub-specialities due to expanding knowledge. I remember a 1930s medicine book whose only description of haemoglobin was "a red pigment that carries oxygen". Now there are whole libraries on haemoglobin and its pathologies. Histopathology has seen the almost total ditching of electron microscopy and emergence of immunohistochemistry to help with diagnosis, and genetic techniques promise even greater diagnostic accuracy.

TS: WHAT DOES YOUR WORK ENTAIL EXACTLY?

Like surgery and anaesthesia, surgical pathology is a potentially dangerous speciality. Mistakes in surgical pathology diagnosis can have very serious consequences to the patient, such as unnecessary drastic surgery, administering the wrong chemotherapy or even unnecessary chemotherapy and/or radiotherapy.

TS: HOW HAS YOUR WORK SHAPED YOUR PRESENT INTERESTS?

I am Visiting Chairman to the Academy of Nutrition Medicine in London and this stems from my interest in nutrition, lifestyle and chronic disease and life expectancy. Deaths from heart attacks in Malta are almost twice the European average, where France has the least. My interest in atherosclerosis (one of two main causes of death in the West) was sparked at St George's Hospital where a number of the senior pathologists had researched the subject. I was appointed one of Malta's scientific delegates to the European Medicines Agency (FDA's European counterpart) and served for almost a decade. It was interesting to contribute to the debates on whether a proposed medicinal product was expected to work as the pharmaceutical company claimed in its dossier.

TS: AND THEN THERE IS TEACHING ...

I have taught pathology in London and in Malta, and I learned that undergraduate teaching is far more difficult than postgraduate. The product of undergraduate teaching is supposed to be safe family doctors and safe house and casualty officers. So what should be included in the 5-year medical course, when medical knowledge is expanding so fast, presents a great challenge to medical educators. I was lucky in having experienced undergraduate teaching at St George's Hospital in 1974. It was then called "topic teaching" (now often referred to as "problem-based learning"), and was organised by Professor Dornhorst of the internal medicine department (and of "pink puffer and blue bloater" fame). These whole class one-hour teaching sessions were chaired by Dornhorst with accompanying

With his wife at a MAM dinner a couple of years ago

teachers from the surgical, radiology and pathology departments. So, for example with peptic ulcer, the whole gamut of clinical presentation, radiology, medical and surgical treatment, and pathology, would be covered in one hour, without the need for more formal lectures on that subject by the various departments. It also avoided different departments teaching different things on the same subject, which was confusing to students. In the Dornhorst model, medical controversies where discussed by the teachers in the same "topic teaching" session. At the Malta medical school, I was tasked to review the curriculum of the three clinical years (Professor Alex Felice was tasked with the preclinical curriculum). Students had complained of too many boring lectures with no interaction, and contradictory information from different teachers. I tried to cut down on lectures and introduce teaching sessions with a combined clinical and pathology teacher. It worked very well with some clinical teachers but not with others who wanted to continue with their old-fashioned ways. I also did away with the so-called "pathology practical" classes where students used to look down microscopes and not know what they were looking at – a total waste of time. The family doctor or casualty officer no longer looks down a microscope to diagnose his patients – he/she gets a report from the laboratory and needs to know exactly what the pathology reports mean – nothing else.

TS: WHAT ISSUES WORRY YOU VIS-A-VIS THE WAY DOCTORS ARE TRAINED?

Medical school teachers easily forget that the product of the undergraduate course is supposed to be a safe house office and family doctor, and not an anatomist, surgeon, cardiologist, pathologist, etc. Three months anatomy teaching and dissection of the upper limb, for example, is suitable for trainee orthopaedic surgeons and not for family doctors. Compare the one-hour topic teaching on peptic ulcer in 1974 St George's Hospital with the 23 peptic ulcer surgery lectures we suffered in Malta a few years earlier. Also, some Maltese teachers seemed to believe that the higher the failure rate the higher the teaching standard, rather than the other way round. Another negative result of conventional medical school teaching all over the world is, as Dean Ornish (California Professor of Medicine) confirms, doctors whose knowledge and experience consist of only pharmaceutical drugs and surgical procedures with little or no nutritional medicine knowhow. Ornish is a conventional cardiologist who also has complimentary medicine experience. He has demonstrated that his programme of dietary modification, regular exercise and stress management can actually reverse coronary heart disease. With urology colleagues he has also shown that his diet and lifestyle programme can halt and to an extent reverse low grade prostate cancer.

TS: WHICH ASPECTS OF PATHOLOGY RESEARCH DO YOU FEEL HAVE BEEN MOST SIGNIFICANT?

Electron microscopy and DNA studies established that the cause of warts are Human Papilloma Viruses, and that some of them are the cause of ano-genital and some oro-pharyngeal cancers. The cause of most peptic ulcers has been established to be a bacterial infection curable with antibiotics, and not with surgery as in the past. We are coming round to recognising that the main factor in the causation of atherosclerotic cardiovascular disease is not animal fats but high glycaemic carbohydrates.

TS: DOES KEEPING ABREAST OF RESEARCH ALLOW YOU TIME FOR RELAXING ACTIVITIES?

I have to admit I don't read fiction as trying to keep up–to-date with pathology and medical advances, and with local and world events, occupies a lot of my time. I enjoy gardening and I'm interested in food and wine. With others, we continue to organise a 17-year old blind-tasting wine and dining club, called "*Il- Qatra*", which has a membership of over 70. I am on the Council of the local Chaine des Rotisseurs, a branch of a worldwide dining club (the oldest in the world), I have just been appointed fellow of The Today Public Policy Institute, a local think tank, and the National Association of Service Pensioners also takes up some of my time. Perhaps many consultants don't realise that if they have contributed significantly to a work-place pension of another country's health system, their Maltese social security pension they are paying for will eventually be correspondingly deducted – unless the Maltese government is made to change the social security law which permits this iniquity. Hello, is the MAM listening?

I READ THE SYNAPSE BECAUSE...

It provides useful, practical, non-esoteric information – there is always something of interest in every issue.

INFLAMMATORY BOWEL DISEASE - CT AND MR DIAGNOSIS

PIERRE VASSALLO

The term inflammatory bowel disease refers to two main entities, ulcerative colitis (UC) and Crohn's disease (CD). The aetiology of these two conditions is uncertain. However, it has been suggested that they are the result of genetic factors leading to an abnormal immune response within the bowel wall to normal bowel contents. UC appears to precede CD in new cases. The incidence of IBD is increasing and there is a higher incidence of IBD in the developed world, which appears to suggest that a westernized diet may be a contributing risk factor.

Endoscopy is one of the main investigations used to diagnose inflammatory bowel disease. Two techniques are available, either conventional push endoscopy or capsule endoscopy. Push endoscopy has one major limitation in that most of the small intestine is inaccessible with this technique; the proximal jejunum and the terminal ileum may be accessible, but the intervening small bowel segments are not. One advantage of push endoscopy is that it allows lesion biopsy. Capsule endoscopy does visualize the whole bowel, but there is a significant risk of capsule retention particularly in the more severe cases of CD due to bowel strictures. Capsule endoscopy does not allow biopsy.

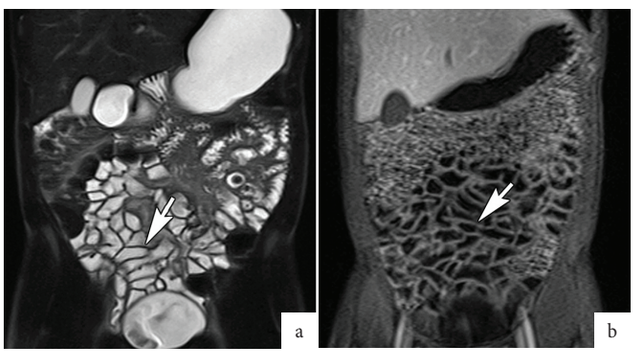

Figure 1. a. Coronal T2-w image showing normal thin small intestinal bowel walls with low signal intensity (arrow). b. Coronal contrast-enhanced T1-w scan showing normal thin uniformly-enhancing small bowel walls (arrow).

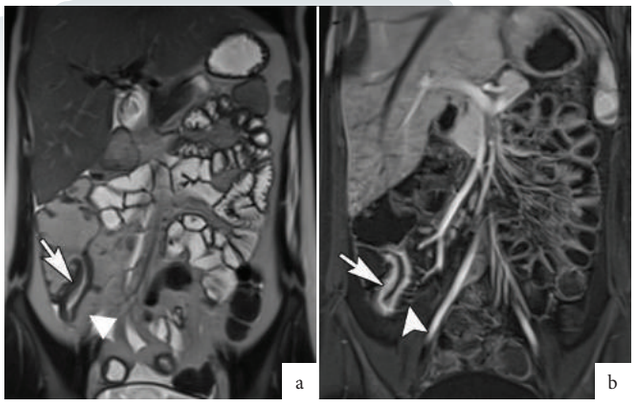

Figure 2. a. Coronal T2-w image shows thickening of the bowel wall (arrow) and proliferation of fat separating the bowel from adjacent segments (arrowhead). b. Coronal delayed post IV contrast T1-w image showing marked enhancement of the inflamed wall of the terminal ileum (arrow) with enhancement of the vasa recta (arrowhead) often referred to as the comb sign.

MR Enterography is a non-invasive imaging method that does not use ionizing radiation and that evaluates the whole GI tract. MR Enterography also depicts wall thickness and any extra intestinal manifestations of CD; it detects strictures, fistulae, mesenteric infiltration, lymphadenopathy and involvement of other organs. The detection of deep mural and extra intestinal manifestations and the presence of small bowel involvement are crucial in the distinction of CD from UC. If biopsy is deemed necessary, MR Enterography may help guide the endoscopist to the best location for biopsy. MR Enterography is valuable in assessing those bowel segments that are not accessible to endoscopy due to the presence of bowel strictures.

MR Enterography is performed using multiple imaging sequences including T2-weighted (Fig 1a), T1-weighted both before and after IV contrast administration (Fig 1b) and Diffusion Weighted Imaging (DWI) scans. Oral contrast

material is given to outline the bowel wall one hour before starting the scan and IV medication is administered immediately before and during the exam to reduce bowel motility.

CD is a chronic relapsing/remitting inflammatory disease of the bowel that affects all bowel wall layers and can involve any part of the gastro-intestinal (GI) tract in a patchy multi-segmental fashion; this has led to the term *skip lesions*. The bowel segments most commonly involved by CD are the terminal ileum and the proximal colon. This contrasts with UC, which involves only the mucosal layer of the colon in one continuous segment. However, CD may occasionally involve only the colon.

The most common symptom of IBD is diarrhea. Abdominal pain, mild fever and weight loss may also occur. Overt GI bleeding is more common in UC than in CD; in CD, GI bleeding is usually occult and leads to anaemia. Clinical manifestations that occur with CD (but not UC) include perianal skin tags, fissures and abscesses, intestinal obstruction and extra-intestinal diseases in the skin, bile ducts, liver, bones and joints, eyes and kidneys.

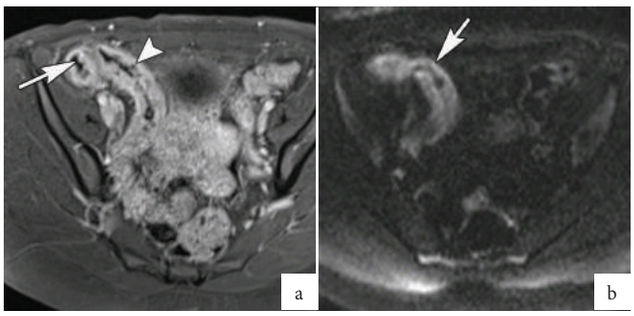

Figure 3. a. Transverse contrast enhanced T1-w image showing an enhancing terminal ileum with mucosal protrusions (arrow) and ulcerations (arrowhead). b. Same case showing diffusion restriction on DWI as increased signal on high B-value image (arrow).

The pathological changes seen in CD have been divided into four stages: acute inflammation, fistulisation/perforation, fibro-stenosis and reparative/regenerative stage. On MR Enterography, it is common to observe multiple (skip) lesions in different stages at any one time.

The earliest pathological finding of CD is the aphthous ulcer; this results from inflammation causing breakdown of the mucosal lining. It usually occurs over a lymphoid follicle and non-caseating granuloma formation may occur. Detection of these findings is key to reaching a histologic diagnosis of CD.

CROHN'S DISEASE IS ASSOCIATED WITH AN INCREASED INCIDENCE OF COLORECTAL CANCER AND LYMPHOMA

MR Enterographic findings of early CD include bowel wall thickening (>2mm for the small intestine and >3mm for the colon) with increased signal within the wall on T2-weighted images (Fig 2a). Contrast enhancement in T1-weighted images (Fig 2b and 3a) and diffusion restriction of DWI scans (Fig 3b) is seen within the inflamed segments of the bowel wall. Oedema of the bowel wall may result in bowel stenosis with intestinal obstruction; it is important to distinguish this from stenosis occurring due to fibro-stenosis as management differs. Obstruction due to acute inflammation is treated with anti-inflammatory medication (Fig 4), while that due to fibro-stenosis may require surgical intervention.

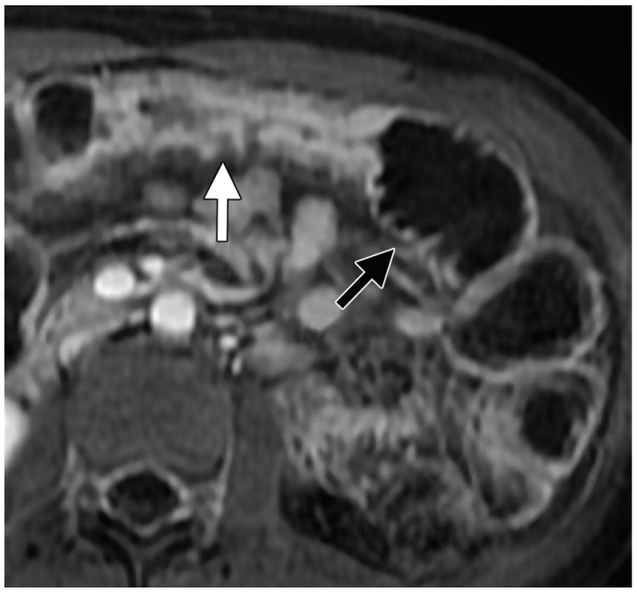

Figure 4. Transverse contrast enhanced T1-w image shows bowel wall thickening and enhancement (white arrow) and proximal bowel dilatation due to obstruction (black arrow).

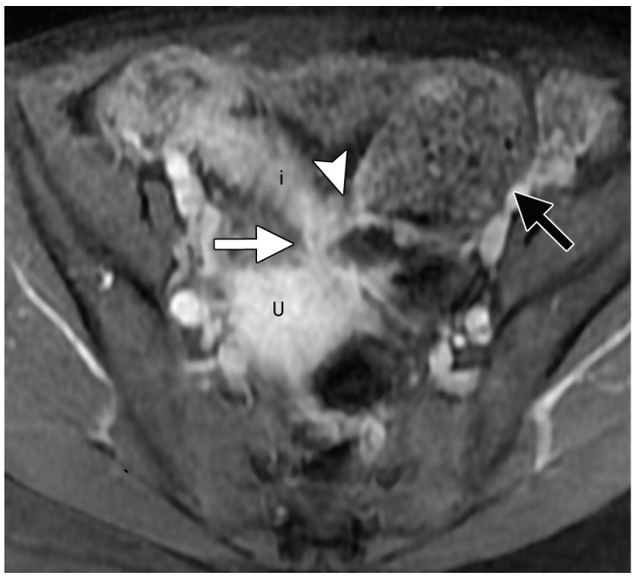

Figure 5. Transverse T1-w MR entrograph shows a fistula (white arrow) between the ileum (i) and uterus (U), a short-segment stricture (arrowhead) just proximal to the fistula and more proximal dilatation of the small bowel (black arrow).

MR ENTEROGRAPHY IS USEFUL TO ASSESS THOSE UNREACHABLE SEGMENTS OF COLON LOCATED PROXIMAL TO A STENOSIS, AS WELL AS TO LOOK FOR EXTRA-COLONIC EVIDENCE OF MALIGNANT DISEASE

Fistulae and sinus tracts with abscess formation occur in around a third of patients with CD. A fistula may occur between two bowel loops or may occur to the skin or any other viscus such as the uterus, vagina or bladder. Endoscopy cannot assess the degree of the extraluminal extension. MR Enterography clearly depicts sinus and fistulous tracts (Fig 5) as well as any associated intra-abdominal abscess.

Intestinal stenosis due to fibro-stenotic disease is also readily detected by MR Enterography; a thickened intestinal wall with low T2 signal, moderate contrast enhancement on T1-w scans, no mesenteric infiltration or vasa recta enhancement and proximal intestinal dilatation are features of fibro-stenotic disease (Fig 6).

CD is associated with an increased incidence of colorectal cancer and lymphoma. Asymmetric thickening of the bowel, a mass-like lesion, non-response to treatment and enlarged mesenteric lymph nodes >1cm in diameter, should all raise the suspicion of malignant disease.

In contrast, UC is usually characterized by inflammation restricted to the mucosal layer of the colonic wall affecting one contiguous bowel segment. Occasionally, inflammation may extend into the distal ileum, a condition referred to as *backwash ileitis*. Characteristic MR Enterographic findings include sparing of the small intestine, wall thickening in the colon particularly the rectum and sigmoid colon with high T2 signal in the mucosal layer (Fig 7a) and contrast enhancement in the mucosal layer (Fig 7b) with no abnormality in the mesentery or the vasa recta.

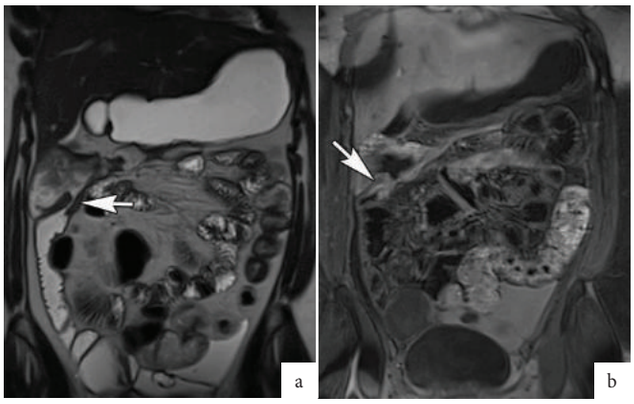

Figure 6. a. Coronal T2-w MR Enterography shows wall thickening (arrow) with low signal at the site of ileo-colic anastomosis; the patient had undergone partial ileo-colectomy. b. Coronal contrast enhanced T1-w image show only moderate wall enhancement (arrow) both no mesenteric infiltration or vasa recta enhancement indicative of a fibro-stenotic stage of CD.

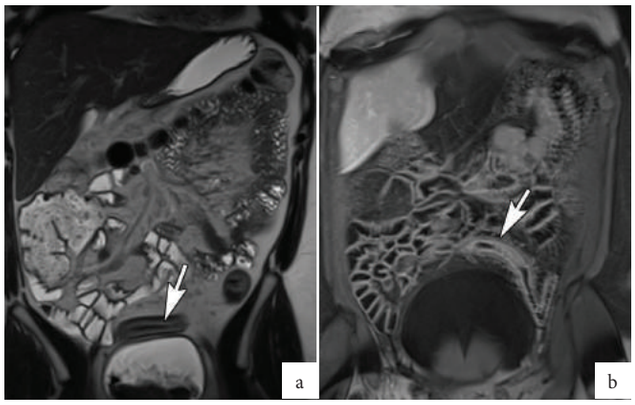

Figure 7. a. Coronal T2-w MR Enterography in a patient with UC shows sigmoid colonic wall thickening with high signal in the mucosal layer (arrow). b. Coronal contrast enhanced T1-w image shows mucosal enhancement (arrow) but no involvement of the outer bowel wall, mesentery or vasa recta.

Endoscopy will usually cover all diseased bowel in UC, however occasionally strictures impending scope entry may also occur. Strictures with UC need detailed investigation as colon-rectal cancer is also known to occur more commonly in these patients. MR Enterography is useful to assess those unreachable segments of colon located proximal to a stenosis as well as to look for extra-colonic evidence of malignant disease.

In conclusion, endoscopy and MR Enterography are complementary examinations used in the diagnosis and management of IBD. They enable accurate characterization and classification of IBD in most patients and are extremely useful in guiding therapy of these conditions.

2 linked challenges, 1 simple solution

TRIVERAM®

Atorvastatin + Perindopril arginine + Amlodipine

1 tablet once daily

COMPOSITION: Triveram 20mg/5mg/5mg, 40mg/10mg/10mg film-coated tablets contain 20mg atorvastatin (ator) / 5mg perindopril arginine (per) / 5mg amlodipine (amlo), 40mg ator/10mg per/10mg amlo. Contains lactose as excipient. **INDICATIONS*:** Substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia, in adult patients adequately controlled with atorvastatin, perindopril and amlodipine given concurrently at the same dose level. **DOSAGE AND ADMINISTRATION*:** One tablet once daily before a meal in the morning. Triveram is not suitable for initial therapy. If a change of posology is required, the dose could be modified or individual titration with free combination may be considered. ***Elderly and patients with renal failure:*** frequent monitoring of creatinine and potassium. Clcr < 60 ml/min: not suitable. ***Hepatic impairment:*** should be used with caution. Triveram is contraindicated in patients with active liver disease. ***Children and adolescents:*** should not be used. **CONTRAINDICATIONS*:** Hypersensitivity to the active substances or to any other ACE inhibitor or dihydropyridine derivatives or statin or to any of the excipients, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section PREGNANCY* and BREASTFEEDING*), severe hypotension, shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g., hypertrophic obstructive cardiomyopathy and high grade aortic stenosis), haemodynamically unstable heart failure after acute myocardial infarction, history of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy, hereditary or idiopathic angioedema, concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m²) (see section INTERACTIONS*). **WARNINGS*:** ***Special warnings and precaution for use: Liver effects:*** liver function tests should be performed periodically and in case of transaminase levels increased, the patient should be monitored until resolution. Stop treatment if jaundice or marked elevations of hepatic enzymes (serum transaminases exceeding 3 times the upper limit of normal) and in patients with active liver disease. Use with caution in patients with hepatic impairment, who consume alcohol and/or have history of liver disease. ***Skeletal muscle effects:*** stop treatment if elevation of CK levels > 10 x ULN or muscular symptoms with elevation of CK level > 5 x ULN occur, or if rhabdomyolysis is suspected. Caution should be exercice when Triveram is used with certain medicinal products that may increase the plasma concentration of atorvastatin and then the risk of rhabdomyolysis such as potent inhibitors of CYP3A4 or transport proteins (e.g ciclosporine, ketoconazole, ritonavir…). ***Interstitial lung disease:*** if suspected, treatment should be discontinued. ***Diabetes Mellitus:*** In diabetic patients, glycaemic control should be closely monitored during first month of treatment. Patients with cardiac failure: use with caution. Hypotension: monitor blood pressure, renal function and potassium in patients at high risk of symptomatic hypotension (volume depleted or who have severe renin-dependent hypertension) or with symptomatic heart failure (with our without renal insufficiency), or with ischaemic heart or cerebrovascular disease. A transient hypotensive response is not a contraindication to further doses once the blood pressure has increased after volume expansion. ***Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:*** use with caution and see **CONTRAINDICATIONS**. ***Kidney transplantation:*** no expetience in case of recent transplantation. ***Renal impairment:*** monitor potassium and creatinine; individual dose titration with the monocomponents recommended if Clcr < 60 ml/min. In patients with renal artery stenosis, blood urea and creatinine may increase; with renovascular hypertension, risk of severe hypotension and renal insufficiency. Amlodipine may be used at normal doses in patients with renal failure. Amlodipine is not dialysable. ***Haemodialysis patients:*** use with caution. ***Hypersensitivity/Angioedema:*** stop treatment and monitor until complete resolution of symptoms. Angioedema associated with laryngeal oedema may be fatal. ***Anaphylactoid reactions during low-density lipoproteins (LDL)*** apheresis: rarely, patients have experienced life-threatening anaphylactoid reactions, temporarily withhold treatment prior to exams. Anaphylactoid reactions during desensitisation: temporarily withhold treatment prior to exams. These reactions reappeared upon inadvertent rechallenge. ***Neutropenia/agranulocytosis/thrombocytopenia/anaemia:*** extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treated with allopurinol or procainamide, periodic monitor of white blood cell counts advised. ***Race:*** perindopril may be less effective and cause a higher rate of angioedema than in non-black. ***Cough:*** resolves after discontinuation. ***Surgery/Anaesthesia:*** stop treatment one day prior to surgery. ***Hyperkaliemia:*** frequent monitoring of blood potassium if renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, dehydratation, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics and potassium salts or supplements. ***Combination with lithium:*** not recommended. ***Dual blockade of the renin-angiotensin-aldosterone system (RAAS):*** concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS is therefore not recommended. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. ***Galactose intolerance/glucose-galactose malabsorption/Lapp lactase deficiency:*** should not be taken. **INTERACTIONS*:** Contraindicated: Aliskiren (in diabetic and impaired renal patients). ***Not recommended:*** CYP3A4 inhibitors, aliskiren, concomitant therapy with ACE inhibitor and angiotensin-receptor blocker, estramustine, lithium, potassium-sparing diuretics (e.g. triamterene,amiloride, eplerenone, spironolactone), potassium salts, dantrolene (infusion), grapefruit or grapefruit juice. ***Precautions:*** CYP3A4 inducers, digoxin, ezetimibe, fusidic acid, gemfibrozil / fibric acid derivatives, transport protein inhibitors, warfarin, antidiabetic agents (insulins, oral hypoglycaemic agents), baclofen, non-steroidal anti-inflammatory medicinal products (NSAIDs) (including aspirin ≥ 3 g/ day), colchicine, colestipol, oral contraceptives, gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin), sympathomimetics, tricyclicantidepressants/ antipsychotics/anesthetics, gold, digoxin, atorvastatin, warfarin or cyclosporine, tacrolimus, antihypertensive agents and vasodilators. **PREGNANCY AND BREASTFEEDING*:** Triveram is contraindicated during pregnancy and lactation. **FERTILITY*:** Reversible biochemical changes of spermatozoe in some patients treated by calcium channel blockers. **DRIVE AND USE MACHINES*:** May be impaired if dizziness, headache, fatigue, weariness or nausea. Caution is recommended especially at the start of treatment. **UNDESIRABLE EFFECTS*:** ***Very common:*** Oedema. ***Common:*** nasopharyngitis, hypersensitivity, hyperglycaemia, somnolence, dizziness, headache, dysgeusia, paraesthesia, vertigo, visual impairment, diplopia, tinnitus, palpitations, hypotension (and effects related to hypotension), flushing, pharyngolaryngeal pain, epistaxis , cough , dyspnoea, nausea, vomiting, abdominal pain upper and lower, dyspepsia, diarrhoea, constipation, change of bowel habit, flatulence, rash, pruritus, joint swelling, ankle swelling, pain in extremity, arthralgia, muscle spasms, myalgia, back pain, asthenia, fatigue, liver function test abnormal, blood creatine kinase increased. ***Uncommon:*** Rhinitis, eosinophilia, hypoglycaemia, hyponatraemia, hyperkalaemia reversible on discontinuation, anorexia, insomnia, mood altered (including anxiety), sleep disorder, depression, nightmares, tremor, syncope, hypoaesthesia, amnesia, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vision blurred, tachycardia, vasculitis, bronchospasm, dry mouth, pancreatitis, eructation, hepatitis either cytolytic or cholestatic, urticaria, purpura, skin discolouration, hyperhidrosis, exanthema, alopecia, angioedema, pemphigoid, photosensitivity reactions, neck pain, muscle fatigue, micturition disorder, nocturia, pollakiuria, renal failure, erectile dysfunction, gynecomastia, chest pain, pain, malaise, oedema peripheral, pyrexia, blood urea increased, blood creatinine increased, weight increase, white blood cells urine positive, weight decrease, fall. **Rare:** Thrombocytopenia, confusional state, neuropathy peripheral, cholestasis, stevens-johnson syndrome, toxic epidermal necrolysis, erythema multiforme, myopathy, myositis, rhabdomyolysis, tendonopathy sometimes complicated by rupture, hepatic enzymes increased, blood bilirubin increased. ***Very rare:*** Leucopenia/neutropenia, agranulocytosis or pancytopenia, haemolytic anaemia in patients with a congenital deficiency of g-6pdh, haemoglobin decreased and haematocrit decreased, anaphylaxis, hypertonia, hearing loss, myocardial infarction secondary to excessive hypotension in high-risk patients, angina pectoris, stroke possible secondary to excessive hypotension in high-risk patients, eosinophilic pneumonia, gastritis, gingival hyperplasia, jaundice, hepatic failure, exfoliative dermatitis, renal failure acute. ***Not known:*** immune-mediated necrotizing myopathy, extrapyramidal disorder (extrapyramidal syndrome). **OVERDOSE*, PROPERTIES*:** Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase. Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. **PRESENTATION:** Box of 30 tablets Triveram 20mg/5mg/5mg, 40mg/10mg/10mg. **LABORATOIRES SERVIER**, 50 rue Carnot, 92284 Suresnes cedex France. www.servier.com **For complete information, please refer to the Summary of Product Characteristics. Jan 2016**

Enterogermina

PROBIOTIC

ANTIBIOTIC RESISTANT[1-3]

THERMO RESISTANT[1]

GASTRO/BILE RESISTANT[4-6]

Bacillus clausii spores

Resistant to chemical and physical factors, able to arrive at the enteric level and germinate resulting in metabolically active cells.[1-7]

For the treatment and prophylaxis of intestinal dismicrobism and consequent endogenous vitamin deficiency.[1]

1. Enterogermina SmPC
2. Bozdogan B et al. Antimicrob Agents Chemother 2003;47:1343-1346.
3. Bozdogan B, Galopin S, Leclercq R. Appl Environ Microbiol 2004;70:280-284.
4. Ciffo F et al. Farmaci e Terapia 1987;4:163-169.
5. Duc le H et al. Appl Environ Microbiol 2004;70:2161-2171.
6. Cenci G. Trotta F, Caldini G. J Appl Microbiol 2006;101:1208-1215.
7. Mazza P. Boll Chim Farmaceutico 1994;1:3-18

SANOFI

NAME OF THE MEDICINAL PRODUCT ENTEROGERMINA 6 billion/2 g powder for oral suspension **QUALITATIVE AND QUANTITATIVE COMPOSITION** *One sachet contains:* Active ingredient: 6 billion polyantibiotic-resistant *Bacillus clausii* spores **PHARMACEUTICAL FORM** Powder for oral suspension. Therapeutic indications Treatment and prevention of intestinal dysmicrobism and subsequent endogenous avitaminosis. Coadjuvant treatment to restore intestinal microbial flora altered during treatment with antibiotics or chemotherapy. Enterogermina 6 billion is indicated for use in adult patients only. **Dosage and method of administration** Adults: 1 sachet a day to be dissolved in water. This medication is for oral use only. **Contraindications** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use.** During treatment with antibiotics, it is recommended that the preparation be administered between antibiotic administrations. This medication is for oral use only. Do not administer in any other way. Incorrect use of the medicinal product has caused severe anaphylactic reactions such as anaphylactic shock. **Interaction with other medicinal products and other forms of interaction** No interaction studies have been performed. **Fertility, pregnancy and lactation** There are no contraindications for use of the preparation during pregnancy or lactation. **Effects on ability to drive and use machines** Enterogermina has no influence on the ability to drive and use machines. **Undesirable effects** Skin and subcutaneous tissue disorders: unknown: hypersensitive reactions, including rash, hives and angioedema. **Overdose** No cases of overdose have been reported. **List of excipients** Heavy kaolin, microcrystalline cellulose, mannitol, sodium saccharin, citrus flavour, colloidal anhydrous silica. **Incompatibilities** None. **Shelf life** 3 years. **Special precautions for storage** Store below 30°C. **Nature and contents of container** Lithographed cardboard box containing 10 sachets. **Special precautions for disposal and other handling** No special instructions. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. **MARKETING AUTHORISATION HOLDER** Sanof S.p.A. – Viale L. Bodio, 37/b – IT-20158 Milano (Italy) **MARKETING AUTHORISATION NUMBERS** Box of 10 sachets AIC 013046091 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** First authorisation date: 25 October 2013 **DATE OF REVISION OF THE TEXT** December 2015. **NAME OF THE PRODUCT ENTEROGERMINA** 2 billion / 5 ml oral suspension ENTEROGERMINA 2 billion hard capsules **QUANTITATIVE COMPOSITION** *One vial contains:* Active ingredient: Polyantibiotic-resistant spores of Bacillus clausii 2 billion *One capsule contains:* Active ingredient: Polyantibiotic-resistant spores of Bacillus clausii2 billion **Therapeutic indications** Treatment and prevention of intestinal dismicrobism and consequent endogenous vitamin deficiency. Adjuvant therapy to restore the microbial flora in the intestine, altered during a course of antibiotics or chemotherapy. Treatment for acute and chronic gastroenteritis in children being breastfed, caused by poisoning or intestinal dismicrobism and vitamin defciency. **Dosage and method of administration** Adults: 2-3 vials a day or 2-3 capsules a day. Children: 1-2 vials a day or 1-2 capsules a day. Children being breastfed: 1-2 vials a day. Vials: take at regular intervals. Drink the content of the vial as it is or dilute it with water or other drinks (e.g. milk, tea, orangeade). Capsules: swallow with a sip of water or other drink. Small children may fnd it difcult to swallow the hard capsule: we recommend children take the oral suspension. This medicine is for oral use only. Do not inject the medicine or take it in any other way. **Contraindications** Hypersensitivity to the active ingredient or any of the excipients. **Special warnings and precautions for use** *Warnings* The presence of corpuscles or tiny particles in the ENTEROGERMINA vials is due to an aggregation of spores of Bacillus clausii; it is not a sign that the product has been altered. Shake the vial before use. *Precautions for use* During a course of antibiotics, it is recommended you take Enterogermina in the interval between one dose of antibiotics and another. **Interactions with other medicines and other forms of interaction** No interaction studies have been conducted. **Pregnancy and breastfeeding** This medicine can be taken during pregnancy or while breastfeeding. **Effects on the ability to drive vehicles and use machinery** Enterogermina does not alter the ability to drive vehicles or use machinery. **Side-effects** When the product was being commercialised, hypersensitivity reactions were reported including rash and hives. **Overdose** No cases of overdose have been reported. **List of excipients** Vials: Purifed water. Capsules: Heavy kaolin, Microcrystalline cellulose, Magnesium stearate, Gelatine, Titanium dioxide (E171) and Purifed water. **Incompatibilities** None. **Shelf life** Vials 2 years. Once the vial has been opened, the medicine should be taken immediately to avoid the suspension becoming contaminated. Capsules 3 years. **Particular precautions for storage** Store below 30°C. **Particular precautions for disposal and other handling instructions** Vials: shake the vial before use. **HOLDER OF THE MARKETING AUTHORISATION** Sanof S.p.A. – Viale L. Bodio, 37/b – IT-20158 Milan (Italy) **NUMBER OF MARKETING AUTHORISATIONS** Box of 10 vials 2 billion AIC 013046038 Box of 12 capsules 2 billion AIC 013046053 **DATE OF THE FIRST AUTHORISATION / AUTHORISATION REVISION** Date of the frst authorisation: Oral suspension 14 November 2001 Capsule 9 December 2004 Date of last revision: 30 July 2008 **TEXT LAST REVISED** October 2014. For further information please contact Sanof Malta Ltd Tel:21413022. MT-BAC-17-02-01