THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

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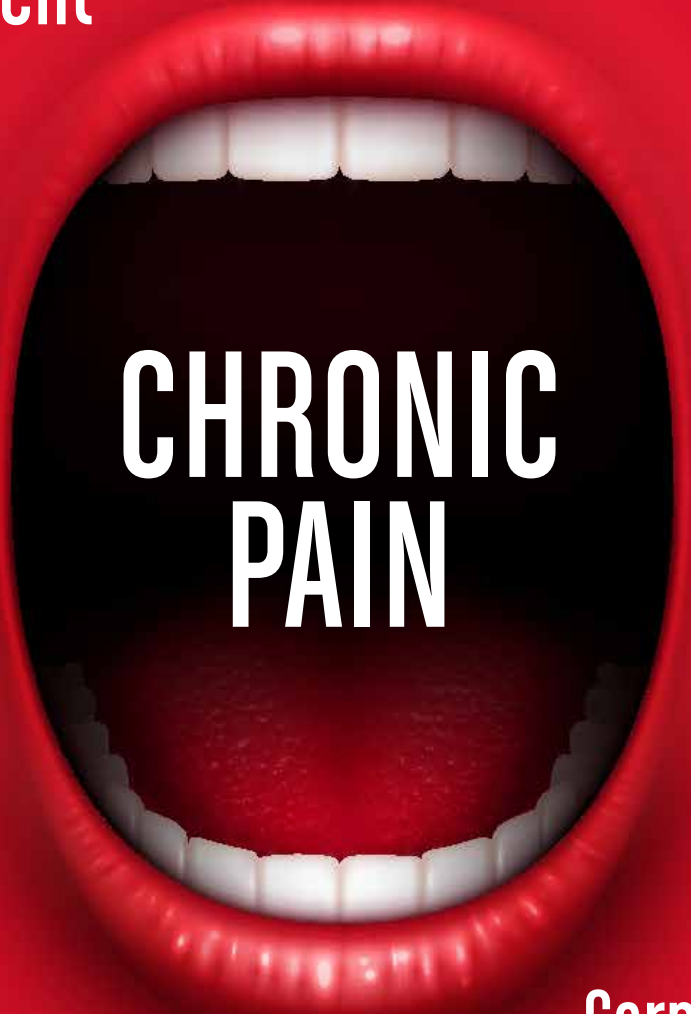
Role of the Microbiome in Health and Disease

US Assessment of RUQ Abdominal Pain



CHRONIC PAIN

How AI will make you rethink Healthcare Today!

Carpometacarpal Osteoarthritis of the Thumb

Augmentin® ES

600 mg/42.9 mg/5 ml

Amoxicillin/Clavulanate Potassium

Powder for oral suspension

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

Spreading infectious energy!

Abridged Prescribing Information: *Please refer to the full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAMES:** Augmentin ES. **ACTIVE INGREDIENTS:** Amoxicillin (as trihydrate) and potassium clavulanate. **PHARMACEUTICAL FORM:** 600mg/42.9mg/5ml powder for oral suspension. **INDICATIONS:** Treatment of acute otitis media & community acquired pneumonia in children aged at least 3 months and less than 40kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY:** 90/6.4mg/kg/day in 2 divided doses. Oral use. Administer with a meal. **CONTRAINDICATIONS:** Hypersensitivity to active substances/penicillins/excipients. History of: severe immediate hypersensitivity reaction to another beta-lactam agent, jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **PRECAUTIONS:** Enquiry of previous hypersensitivity reactions to beta-lactams. Switch to an amoxicillin-only preparation (to be considered for infections proven due to amoxicillin susceptible organism). Convulsions may occur in patients receiving high doses or impaired renal function. Should be avoided if infectious mononucleosis is suspected. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Overgrowth of non-susceptible organisms with prolonged use. Occurrence of a feverish generalised erythema associated with pustula at treatment initiation may be symptom of AGEP (reaction requires discontinuation, contraindicates subsequent administration of amoxicillin). Caution in patients with hepatic impairment. Hepatic events may be associated with prolonged treatment. Antibiotic-associated colitis. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Appropriate monitoring when anticoagulants are prescribed concomitantly. Creatinine clearance less than 30 ml/min (not recommended). Possibility of amoxicillin crystalluria. Potential of incorrect diagnostic test results during treatment *(refer to full SPC for details)*. Contains 2.72mg of aspartame (E951) per ml (source of phenylalanine). Contains maltodextrin (glucose). *Refer to the SPC for full details of precautions.* **PREGNANCY/FERTILITY/LACTATION:** Pregnancy: Use should be avoided unless considered essential by the physician. Lactation: benefit/risk assessment to be considered. **UNDESIRABLE EFFECTS:** Common (≥1/100 to <1/10): mucocutaneous candidosis, diarrhoea, nausea, vomiting. Refer to the SPC for full list of undesirable effects. **LOCAL PRESENTATION:** 100ml glass bottle with plastic measuring spoon. **MARKETING AUTHORISATION NUMBER:** AA1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** November 2017. In order to ensure that this product information reects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131) *REPORTING ADVERSE EVENTS (AEs):* If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

References:

1. Anthony R. White *et al.* Augmentin® amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent Journal of Antimicrobial Chemotherapy (2004) 53, Suppl. S1, i3–i20.
2. Gilbert DN, *et al.* Sanford guide to Antimicrobial Therapy v.3.11 – last updated March 11, 2014. Sperryville; Antimicrobial Therapy, Inc. 2014.
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4. Augmentin ES Summary of Product Characteristics, Nov 2017.

Prepared: June 2018 Job No: MLT_GIB/AES/0001/18b

For more information and dosing instructions:
https://gskpro.com/en-mt/products/augmentin/

HEALTH OUTCOME MEASURES & FUTURE GENERATIONS

EDITORIAL

Recent times have seen an invariable increase in industrially processed products. This has coincided with a rising prevalence of non-communicable diseases. One of the most prominent food processing classification systems is NOVA which categorises foods into four clearly distinct groups according to the extent and purpose of food processing, rather than in terms of nutrients.

GROUP 1 Unprocessed or minimally processed foods	Unprocessed foods include edible parts of plants or of animals and also fungi, algae and water. Minimally processed foods are natural foods altered by processes such as removal of inedible parts or pasteurisation.
GROUP 2 Processed culinary ingredients	Processed culinary ingredients, such as oils, sugar and salt, are substances generally derived from Group 1 foods by processes that include pressing and refining. They are not meant to be consumed by themselves, and are normally used to prepare, season and cook group 1 foods.
GROUP 3 Processed foods	The main purpose of the manufacture of processed foods is to increase the durability of group 1 foods, or to modify or enhance their sensory qualities. Examples include canned fruits as well as cheeses.
GROUP 4 Ultra-processed food and drink products	Ingredients only found in ultra-processed products include additives whose purpose is to imitate sensory qualities of group 1 foods or of culinary preparations of these foods, or to disguise undesirable sensory qualities of the final product. Examples include carbonated drinks, ice-cream, chocolate, chicken nuggets, but also breakfast cereals, fruit yoghurts, plain yoghurt with added artificial sweeteners, and infant formulas.

In recent years a growing body of evidence has associated processed foods with adverse health outcomes. Two large European cohort studies published in May 2019 found positive associations between consumption of ultra-processed foods and cardiovascular disease[1] and all-cause mortality.[2] These findings follow a previous study[3] reporting an association between consumption of these foods and an increased risk of cancer.

The study by Srour et al.[1] reported an association between an absolute 10% increase in ultra-processed food and significantly higher rates of overall cardiovascular disease, coronary heart disease, and cerebrovascular disease. Furthermore, the study by Rico-Campà et al.[2] found a positive dose-response association between consumption of ultra-processed foods and all-cause mortality. Participants in the highest quarter of consumption (>4 servings/day) had a 62% higher all-cause mortality rate than those in the lowest quarter (<2 servings/day).

Obviously it is unrealistic to advise people to avoid ultra-processed foods. Possibly reformulating the nutrient composition of these foods may actually be a more effective way to reduce exposure to risk nutrients, which may actually end up displacing nutritious foods from the diet. Evidence is accumulating which shows that the physical and chemical characteristics of these foods might cause harm by changing the gut microbiome.[4]

Greater emphasis should be done on promoting the availability, and accessibility of unprocessed or minimally processed foods. Various studies have investigated the cost-effectiveness of combining taxes on unhealthy foods and/or subsidies on healthy foods with interesting results, with quite interesting conclusions![5,6]

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1. Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ* 2019;365:l1451.
2. Rico-Campà A, Martínez-González MA, Alvarez-Alvarez I, et al. Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. *BMJ* 2019;365:l1949.
3. Fiolet T, Srour B, Sellem L, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ 2018;360:k322.
4. Zinöcker MK, Lindseth IA. The Western Diet-Microbiome-Host Interaction and Its Role in Metabolic Disease. Nutrients 2018;10:E365.
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OUR COLLABORATORS

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

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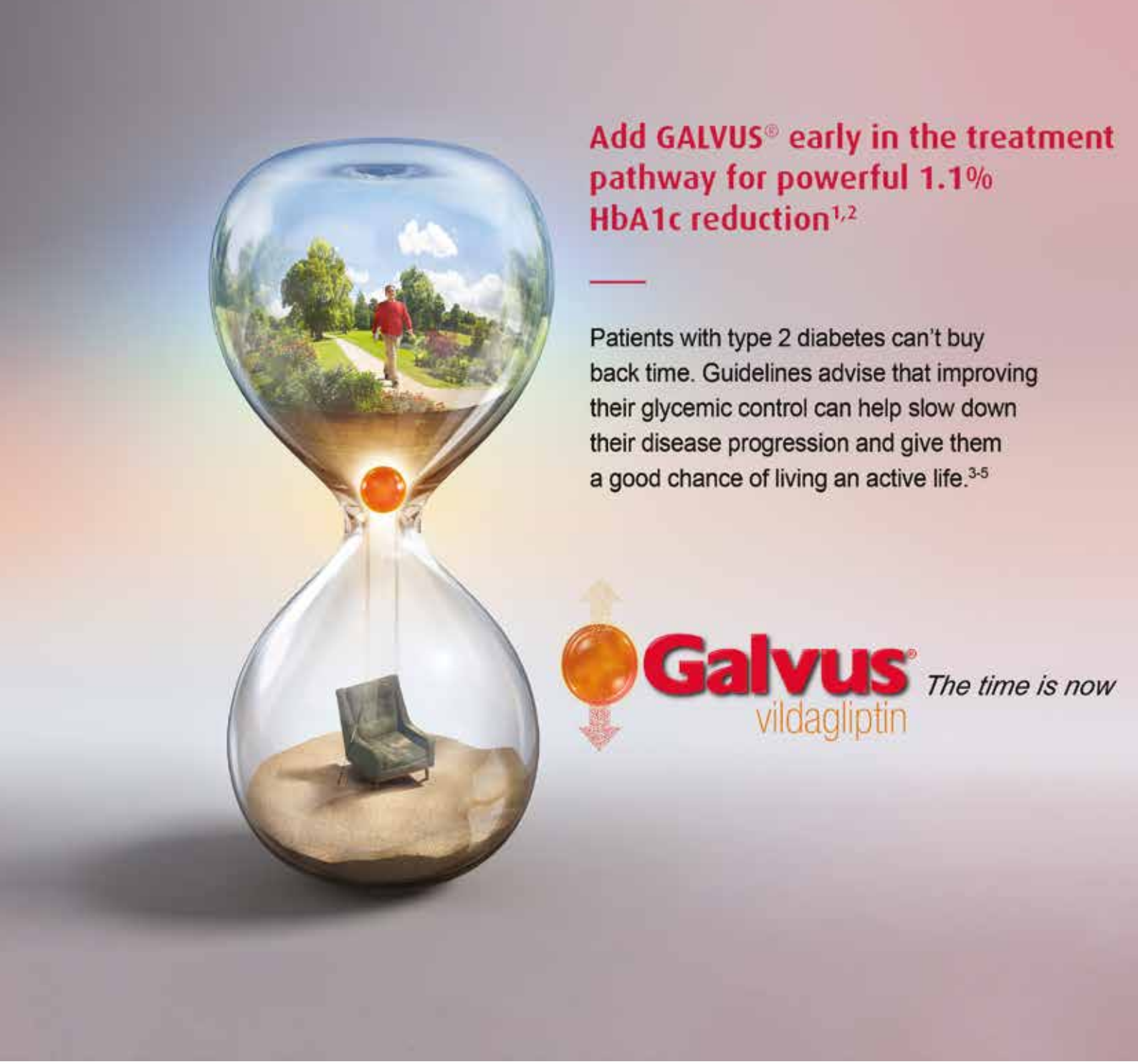

Add GALVUS® early in the treatment pathway for powerful 1.1% HbA1c reduction[1,2]

Patients with type 2 diabetes can't buy back time. Guidelines advise that improving their glycemic control can help slow down their disease progression and give them a good chance of living an active life.[3-5]

Galvus®
vildagliptin

The time is now

Galvus®

PRESENTATION: Each tablet contains 50 mg of Vildagliptin **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: i) As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. ii) As dual oral therapy in combination with: metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. iii) As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. A lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustments are necessary in elderly patients (≥ 65 years). **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding, since no studies on the effect on human fertility have been conducted for Galvus. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors **ADVERSE REACTIONS:** Monotherapy: Common (>1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/003. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2018-MT- GAL-26-APR-2018

References:

1. Novartis Europharm Ltd. Galvus Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas Summary of Product Characteristics
3. Holman RR et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
4. Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38(1):140-149.
5. Garber AJ et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013; 19(2):327-336

Eucreas®

PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 ml/min). Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol due to an increased risk of lactic acidosis, iodinated contrast agents, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angiodema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 30, 60 film-coated tablets MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/021, EU/1/07/425/027. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872 2018-MT-EUC-23-APR-2018

NOVARTIS

GAL AD1 06/19 MT

Galvus® vildagliptin Eucreas®

AUTHORS

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ISSUE GUIDE

TheSynapse

How does your choice of ICS/LABA stand up to a 24-hour world?

Throughout day and night, their **24-hour world** needs an ICS/LABA that lasts. Relvar is the only ICS/LABA providing 24 hours of continuous efficacy from just one daily inhalation,[1] and is superior to ICS/LABAs in helping more patients improve asthma control in everyday clinical practice.*[2]

Relvar 92/22mcg & 184/22mcg are indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.
- patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist.[3]

Please refer to full SmPC for detailed information.

ZINC Code: MLT_GIB/FFT/0005/18 Date of preparation: April 2018

Relvar Ellipta was developed in collaboration with INNOVIVA

RELVAR ELLIPTA
fluticasone furoate/vilanterol

References: 1. Bernstein DI, Bateman ED, Woodcock A, Toler WT, Forth R, Jacques L, *et al.* Fluticasone furoate (FF)/ vilanterol (100/25mcg or 200/25mcg) or FF (100mcg) in persistent asthma. *J Asthma* 2015;52(10):1073–1083. **2.** Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, *et al.* Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open label, parallel group, randomised controlled trial. *Lancet* 2017; doi.org/10.1016/S0140-6736(17)32397-8. **3.** Relvar SmPC, March 2018.

▼RELVAR ELLIPTA ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: Relvar Ellipta. **ACTIVE INGREDIENT:** *92mcg/22mcg dose:* 92mcg fluticasone furoate, 22mcg vilanterol (as trifenatate). *184mcg/22mcg dose*: 184mcg fluticasone furoate / 22mcg vilanterol (as trifenatate). **PHARMACEUTICAL FORM:** Inhalation powder, pre-dispensed. **INDICATIONS:** ***Asthma*** *(92/22mcg dose & 184/22mcg dose):* Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists and patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist. **COPD** (92/22mcg dose): For symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. **POSOLOGY:** *For Asthma*: One inhalation, once daily. *For COPD*: One inhalation of 92/22mcg dose, once daily. 184/22mcg is not indicated for patients with COPD. Relvar Ellipta should be administered at the same time of day, each day. *Refer to full SPC for full dosage recommendations.* **CONTRAINDICATIONS:** Hypersensitivity to active ingredients / excipients. **PRECAUTIONS:** Should not be used to treat acute asthma symptoms or acute exacerbation in COPD; Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing; Caution for use in severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium; Moderate to severe hepatic impairment: 92/22mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions; Systemic corticosteroid effects may occur, particularly at high doses for long periods. Caution in patients with pulmonary tuberculosis or chronic or untreated infections; Blurred vision or other visual disturbances: referral to ophthalmologist for evaluation should be considered; Caution in diabetic patients; Physicians should remain vigilant for possible development of pneumonia in patients with COPD (clinical features overlap); Incidence of pneumonia in asthma common at higher dose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* only if expected benefit to mother outweighs risk to foetus. *Lactation:* consider benefit of breast feeding child and benefit of therapy for woman. *Fertility:* No data. **UNDESIRABLE EFFECTS:** *Very common (≥1/10):* headache, nasopharyngitis. *Common (≥1/100 & <1/10):* pneumonia, upper respiratory tract infetion, bronchitis, influenza, candiasis of mouth and throat. Oropharyngeal pain, Sinusitis, Pharyngitis, Rhinitis, Cough, Dysphonia, Abdominal pain, Arthralgia, Back pain, Fractures, Muscle spasms, pyrexia. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** Inhaler x 30 doses. **MARKETING AUTHORISATION NUMBER:** EU/1/13/886/001-6. **MARKETING AUTHORISATION HOLDER:** Glaxo Group Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** March 2018.

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

REPORTING ADVERSE EVENTS (AEs):
If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Ltd, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)
Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal
Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

HOW AI WILL MAKE YOU RETHINK HEALTHCARE TODAY!

LUCA BONDIN &
PROF ALEXEI DINGLI

Say hi to Mario! Mario, the robot-nurse, will soon start helping out in the distribution of medicines to patients at Mater Dei Hospital. Announced by the Health Minister, Hon. Chris Fearne, the new system is to be fully rolled out by 2021. Welcome to the age of Artificial Intelligence!

Up until a few years ago, the mention of Artificial Intelligence immediately brought to mind images of technology synonymous with science fiction movies. Fast-forward a couple of years, and now everybody knows what Artificial Intelligence is, or has at least come across the term "AI". We are now starting to truly appreciate the benefits AI is affording us across several application areas. One of these areas is the area of healthcare.

An important application is that of early disease detection. Hospitals generate an incredible amount of data that has for years, been left unused. But what if the key to help detect early signs of illnesses in patients is hidden somewhere in that data? When a patient is admitted to a clinic, the first thing a physician does is record the signs and symptoms. The case is then followed by noting down any treatment given and any interventions done, and finally, the outcome of the treatment. This is obviously repeated hundreds of times daily by different doctors. The application of AI has given us the capability to analyse all this data and learn any patterns and correlations in medical data to improve rapid decision-making. What we mean by early disease detection is that if a patient comes into a clinic and states his symptoms, then by using AI, the physician can be presented with an accurate list of causes, and more importantly with an effective treatment plan that has been formulated by taking into consideration what worked well in previous interventions.

Linking to the application of early disease detection is the application of AI in medical imaging. Once again, the enormous amounts of data that a hospital generates, this time in the form of medical images, can be applied to excellent use. In 2016, the American technology company NVIDIA announced an affiliation with the Massachusetts General Hospital Clinical Data Science Centre who aims to serve as a hub for AI applications in healthcare for detection, diagnosis, treatment, and management of diseases. The result of this affiliation was a supercomputer that has been trained to detect anomalies in medical images and can reach accurate conclusions, having previously studied 10 billion already-taken medical images. The number of captured medical images is overgrowing, and the process of analysing these images in time becomes unmanageable for any human, leading to the possibility of mistakes being made. AI offers the opportunity of improving this process by analysing the images faster and detecting any anomalies in a more accurate way.

While perhaps these two applications have become the applications most synonymous with AI in healthcare, we have now started exploring other applications that also focus on the patient who is already receiving some form of treatment as opposed to only prevention or early detection. Particular interest in this area has been shown in the application of Virtual Reality systems that help alleviate some of the pain patients go through during chemotherapy sessions, for example. Such systems are based on the workings of distraction therapy. During a treatment procedure, a patient is immersed in a specially designed virtual world that ensures a patient remains focused on what is happening in the world he is seeing rather than focusing on the pain symptoms. I refer you to the work being done by a US-based company KindVR, who is collaborating with clinics across the US to trial non-invasive systems to help children cope with pain.[1,2] Similar research is also being carried out locally by the Department of AI at the University of Malta in collaboration with the Sir Anthony Mamo Oncology Centre.

Another aspect is clinical bed management which is perhaps one of the major challenges in managing hospitals and this arises from the difficulty to forecast patient flow. It is practically impossible for any human to accurately plan ahead taking into consideration all the variables that can change instantly and which affect the whole scenario. An AI platform can easily analyse enormous chunks of relevant data going back years, and make informed decisions about the future through an analysis of common trends. This means that if the data at hand showed that emergency respiratory admissions peaked on particularly cold winters, then an AI system can be programmed to immediately identify such peaks at a very early stage and issue projections.

AI will never completely replace the human element in healthcare, but its adoption ensures that human activities are genuinely enhanced. AI is here and, more importantly, AI is real … now is the right opportunity to start adopting it!

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ROLE OF THE MICROBIOME IN HEALTH AND DISEASE

DR ALFRED GRECH &
DR MICHAEL BALZAN

ABSTRACT

Understanding the role of the microbiota in health and disease may offer new insights into the factors that start and drive the progression of various diseases, like autism, auto-immune disease, obesity, diabetes, and cancer. In turn, this will offer a platform to stratify the risk of patients for complications and also to deliver new personalised therapeutic strategies.

INTRODUCTION

Lederberg and McCray[1] first defined the term microbiota to describe the microorganisms that live in or on the human body. Such microorganisms are found on the skin and in the eyes, gut, mouth, and vagina. About two-thirds of the human microbiota is hosted in the gastrointestinal tract, which is the largest interface to the external environment.

Approximately 1 kg of bacteria is hosted in the human gut! Overall, that equates to about 9.9 million bacterial genes, with the ratio of host DNA to microbiome DNA being 1:10. It is worth mentioning that these microorganisms are also present earlier in life, in the infant gut. Specifically, research has shown that, during delivery, the infant gut is colonised by the microbiome of the maternal anus, skin, and vagina. In addition, the infant gut is inhabited by the bacteria the neonate is exposed to after birth.[2] Other factors structure the neonatal microbiome in both animal models and humans, including antibiotic treatment and diet.[3]

It is posited that microbiota co-evolved in a mutual relationship with humans. In fact, emergent evidence supports the hypothesis that these microorganisms play an important role in maintaining immunologic, metabolic, and nutritional homeostasis in our bodies. However, there are both beneficial and harmful bacteria. Eubiosis occurs if the beneficial bacteria dominate. In contrast, dysbiosis occurs when the harmful bacteria take over. One of the most common diseases caused by dysbiosis is infection.[4] In some specific cases of dysbiosis, consuming live microorganisms in probiotics may improve or restore the gut flora.

In order to understand these host–microbe interactions, researchers use gnotobiotic animal models; animals in which the bacterial strains and other microorganisms present are known. Studies in both these animal models and humans have associated microbiome signatures with disease and health. Indeed, advances in microbial research have provided insight into the role of the human microbiota in diseases such as autism, auto-immune disease, cancer, obesity and diabetes. In turn, all of this knowledge will offer a platform to deliver new personalised therapeutic strategies in the near future.

AUTISM SPECTRUM DISORDERS (ASD)

In recent years, it has become evident that our gut microbiota has far-reaching implications for our brain development and function. Dysbiosis in the gut have been linked with mood disorders (e.g. depression) and autism spectrum disorders (ASD).[5] Even though genetic inheritance has a role in developing ASD, external influences such as gut microbiota may be equally important. While a cause-effect association has not yet been identified, many gastrointestinal problems including abdominal pain, constipation, and diarrhoea are often concomitant with ASD.[6] Indeed, increasing evidence suggests bi-directional communication between the gut microbiota and the central nervous system (known as the "gut-brain axis"), which may play a role in ASD pathogenesis.

The interplay between gut microbiota and ASD may begin even before birth: factors such as diabetes, maternal obesity, and the taking of antibiotics, affect the pre-birth baby gut microbiota, and may be associated with ASD development. Other neonatal factors, such as birth delivery mode (vaginal vs. caesarean section) and breast-feeding affect gut microbiota diversity and the risk of developing ASD. For example, breast-feeding infants for >6 months has been related to a decreased risk of developing ASD,[7] whereas the risk is increased in children born by caesarean section.[8] Indeed, the gut microbiota of children with ASD is typically of a different composition and diversity than that of children without ASD.[9]

Our understanding of the gut microbiota-ASD relationship has greatly improved. As a result, emergent potential therapies for ASD are increasingly focused on gut microbiota modulation. These have included the use of

prebiotics, probiotics, or diet changes in animal models and ASD individuals. Other possible therapies include faecal microbiota transplantation, which involves delivering faecal microbiota from healthy individuals to those with dysbiotic gut microbiota. Overall, changing the gut microbiota might one day provide effective and risk-free therapies for ASD individuals.

OBESITY AND DIABETES

In both developed and developing nations, obesity is associated with a higher risk for chronic diseases. In particular, it is postulated that obesity is linked with chronic, low-grade inflammation which originates from the adipose tissue and the gut and then spreads to other areas of the body. In the gut, the dysregulation of microbiota can increase endotoxin exposure. In addition, the intestine - a barrier against harmful substances from the external environment - can be compromised by factors such as diet, exercise, gastrointestinal peptides, inflammatory cytokines, and pathogens.

In this regard, Pei et al.[10] have shown that lipid profiles, intestinal barrier function, and innate and adaptive immune responses can be improved by consuming yoghurt. Yoghurt, which is dense in nutrients, can decrease inflammation and enhance gut health. Therefore, while yoghurt benefits individuals with constipation and diarrheal diseases, and those with cardiovascular diseases, hypertension, and lactose intolerance, it also improves the health of obese and diabetic people.

In obese and type 2 diabetic mice, Everard et al. (2014) showed that the probiotic yeast *Saccharomyces boulardii* alters gut microbiota and decreases metabolic features, such as fat mass development, hepatic steatosis, and low-grade inflammation.[11] Similarly, Balakumar et al. (2018)[12] investigated the effect of probiotics of Indian gut origin (*Lactobacillus* spp.) in mice and found that in high-fat diet mice, the probiotic intervention resisted insulin-resistance and diabetes. In general, this could lead to different probiotic treatments in the future.

AUTO-IMMUNE DISEASES

It is known that the gut microbiota plays a role in the development of the lymphoid system.[13] In fact, dysbiosis of gut microbiota also occurs in patients with autoimmune diseases such as Hashimoto's thyroiditis, systemic lupus erythematosus, systemic sclerosis, as well as type 1 diabetes mellitus.

Hashimoto's thyroiditis, or HT, is an organ-specific disorder in which both environmental factors and genetic predisposition are disease triggers. Zhao et al. (2018)[14] performed a systematic comparative analysis of the gut microbiota in HT patients and healthy controls and revealed that HT patients have altered gut microbiota. They also showed that gut microbiota is associated with clinical parameters, therefore suggesting that the composition of the microbiome could be used in disease stratification.

Keep HFrEF patients alive, out of the hospital, and on the right path

The path to slowing disease progression starts with ENTRESTO. Improve survival by reducing the risk of HF events, and give them more time to keep doing what they love.[2,3,4,5]

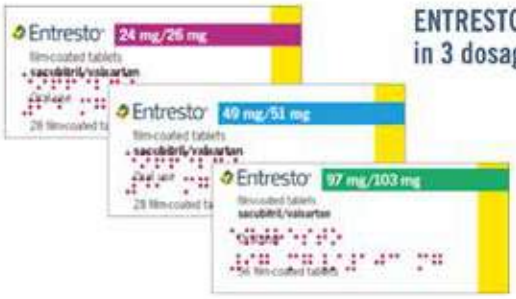
Start ENTRESTO today

GO The starting dose is 24/26 mg or 49/51 mg, twice daily, depending on the patient's current treatment and medical condition[1]

The target dose is 97/103 mg twice daily[1]

Stop using an ACE inhibitor for 1.5 days (36 hours) before starting ENTRESTO[1]

ENTRESTO contains valsartan, and therefore should not be coadministered with another ARB-containing product.



ENTRESTO is available in 3 dosage strengths[1]

Before your NYHA Class II patients with HFrEF leave your office, take action with ENTRESTO—and keep them on the right path.

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, cidosporin), 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, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. 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. 2018-MT-ENT-30-APR-2018

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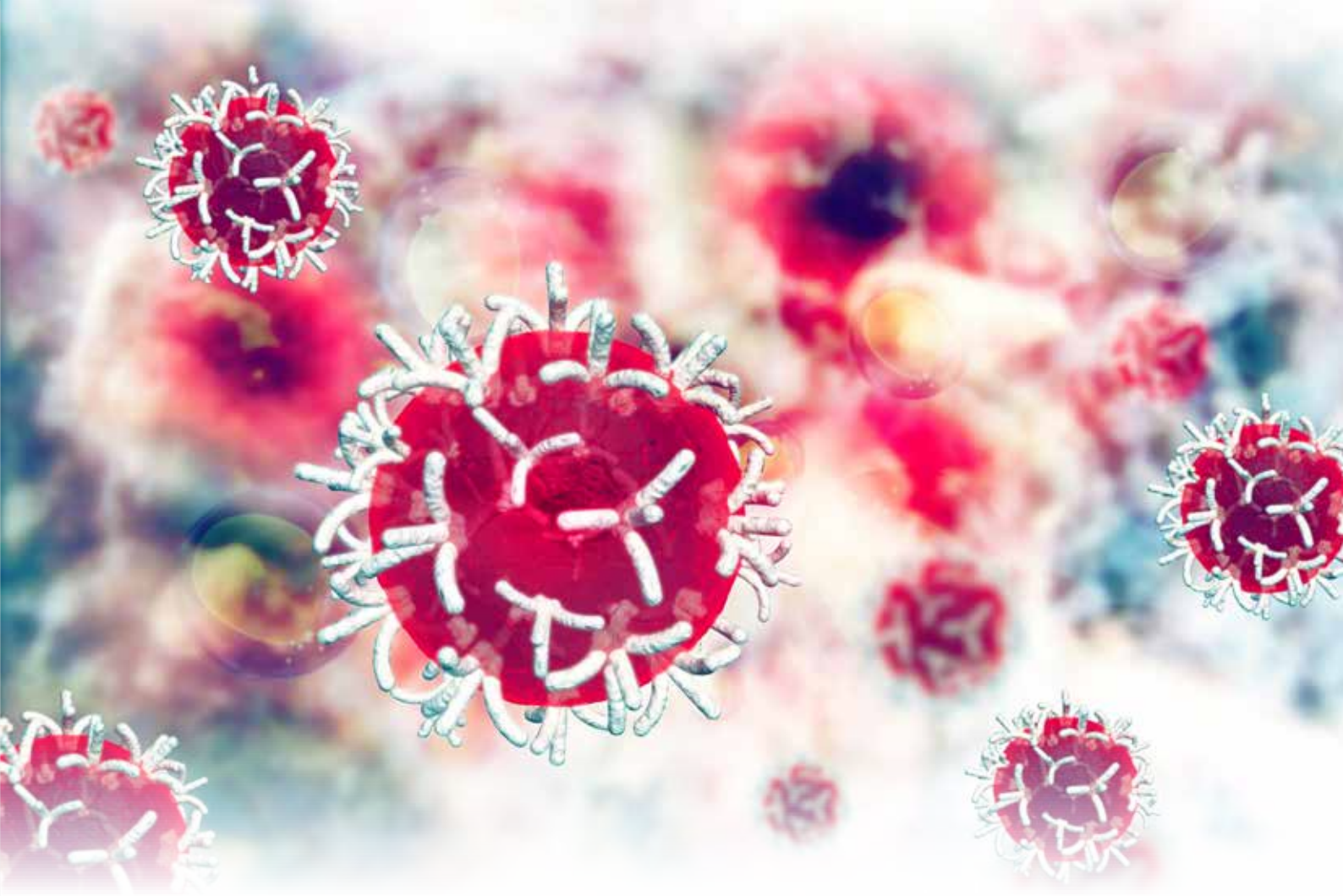
NOVARTIS

Entresto® sacubitril/valsartan



Systemic lupus erythematosus is another autoimmune disease. It is a complex disorder with no known cure, characterised by persistent inflammation. Mu et al. (2017)[15] recently reported that in lupus, the gut microbiota is involved in the pathogenesis of renal dysfunction. Mu et al. used a model of lupus nephritis and found a significant depletion of *Lactobacillales* in the gut microbiota. Intriguingly, increasing the *Lactobacillales* in the gut enhanced renal function and extended survival in mice. Although promising, future studies will determine whether this can be replicated in humans.

CANCER

Over a quarter of a million people each year develop colorectal cancer (CRC). CRC is fundamentally a genetic disease. Specifically, there is an accumulation of mutations in oncogenic genes that foster autonomous colonic epithelial cell proliferation, which over 10 to 40 years, results in colon adenomas. A small number of these adenomas, in some individuals, progress to cancer. Although, it is still unknown what events precipitate the initial mutation(s) or the later progression from adenomas to cancer, the gut microbiome is a main suspect. Indeed, one finds several attempts to associate individual bacterial microbes with CRC in humans.[16,17] Some, based on the 'keystone species' concept, argue that a microbial leader recruits other microbes and these start the fostering events of CRC.[18-20] Thus, it is proposed that over the years, several microbes may be involved and their metabolic activities interact with the host diet, ingested pharmaceuticals, or physiology.

An example of such interplay between the host and gut microbes is observed in bile acid metabolism. The liver secretes the conjugated bile acids, cholic acid and chenodeoxycholic acid. Bacteria can deconjugate these conjugated bile acids producing lithocholic acid and deoxycholic acid. These secondary bile acids are the two principal faecal bile acids and it has been proposed that they may contribute to carcinogenesis. Indeed, back in 2002, Reddy[21] already showed that these faecal bile acids are increased in diets rich in saturated fats and are associated with higher incidence of CRC. Gill and Rowland[22] studied the correlation of dietary fat intake and CRC risk and found that CRC patients, when compared to healthy controls, had elevated faecal lithocholic and deoxycholic acid. Lithocholic and deoxycholic acid were thus proposed that they may be pro-carcinogenic bacterial metabolites. This proposition still stands today and recent studies have shown that they can be pro-inflammatory through the production of reactive oxygen and nitrogen species and NF-κB activation in the cells of intestinal epithelia.[23] In 2018 Le Gall et al.[24] showed that CRC patients had increased faecal concentrations of branched chain fatty acids, besides other potential metabolites that may be responsible for carcinogenesis.

The exact mechanism by which the unconjugated bile acids are responsible for carcinogenesis is still being researched. Barrasa et al.[25] showed *in vitro* that chronic

exposure to deoxycholic acid causes DNA adduct, decreases apoptosis, and augments epithelial cell proliferation. In 2016 Farhana et al.[26] proposed that the unconjugated secondary bile acids modulate muscarinic 3 receptor and Wnt/β-catenin signals and cause cancer stem cells in the epithelial cells of the colon.

However, gut microbiota can also have positive effects on the host physiology. One mechanism is in promoting anti-tumour immunity. Sivan et al.27 studied melanoma growth in mice and found that the commensal *Bifidobacterium* promotes anti-tumour immunity. Indeed, *Bifidobacterium* alone, given orally, controlled tumour growth to the same extent as antibody therapy with programmed cell death ligand 1 (PD-L1) (a check point blockade type of immunotherapy). Similarly, Spranger et al.[28] clinically found that some cancer patients fail to respond to immunotherapy. This could be due to lack of activated T-cell infiltration inside the tumour microenvironment. They propose that intersubject heterogeneity might be responsible and includes variations in the mutations of specific oncogene pathways. But it may also be due to environmental factors like the commensal microbial composition. This has clinical utility in that, by manipulating the gut microbiota, one might modulate cancer immunotherapy and increase the number of patients that respond.

CONCLUSION

Overall, recent research has demonstrated that keeping your gut flora healthy has extensive implications. Though still an emerging field, the gut microbiota may be playing important roles in autism, auto-immune disease, cancer, obesity and diabetes. As a result, research efforts are being focused on developing gut microbiota modulation therapies and using the microbiome for diagnosis and treatment stratification. Hippocrates might have been right when he said that 'All disease begins in the gut' and 'Let food be thy medicine'.

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Helping people with MDD* rediscover the love for life

Treatment with Bupropion led to greater improvement in fatigue scores (p<0.01) in Bupropion remitters (-1.56) as compared to SSRI* remitters (-1.43) in MDD patients at study end point. This improvement was evident from week 4.[1]

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.[2]
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.[2]

WELLBUTRIN XR ABRIDGED PRESCRIBING INFORMATION
Please refer to full Summary of Product Characteristics (SmPC) before prescribing
TRADE NAME: Wellbutrin XR modified release tablets. **ACTIVE INGREDIENT:** Bupropion Hydrochloride, 150mg/300mg. **PHARMACEUTICAL FORM:** Modified release tablet. **INDICATIONS:** Treatment of major depressive episodes. POSOLOGY: Should be swallowed whole with or without food. Tablets should not be cut, crushed or chewed as this may lead to increased risk of adverse effects including seizures. *Adults:* Recommended starting dose is 150 mg, once daily. If no improvement is seen after 4 weeks, dose may be increased to 300 mg, once daily. There should be interval of at least 24 hours between successive doses. Patients should be treated for a sufficient period of at least 6 months. Full antidepressant effect may not be evident until after several weeks of treatment. Insomnia may be reduced by avoiding dosing at bed time. *Children and Adolescents (less than 18 years of age):* not indicated. *Discontinuing therapy:* a tapering off period may be considered. *Refer to full SPC for full Posology details.* **CONTRAINDICATIONS:** Hypersensitivity to Bupropion or any of the excipients; co-administration with other medicinal products containing Bupropion (incidence of seizures is dose-dependent); current seizure disorder or history of seizures; known CNS tumour; patients undergoing withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **PRECAUTIONS:** *Seizures:* Recommended dose should not be exceeded; Caution in patients with predisposing risk factors for seizures such as concomitant administration of medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones, sedating antihistamines), alcohol abuse, history of head trauma, diabetes treated with hypoglycaemics or insulin, use of stimulants or anorectic products; should be discontinued in patients who experience a seizure during treatment; *Interactions:* Bupropion inhibits metabolism by cytochrome P450 2D6; Caution is advised when medicinal products metabolised by P450 2D6 are administered concurrently; Use of Wellbutrin XR, which is an inhibitor of CYP2D6, should whenever possible be avoided during tamoxifen treatment; *Neuropsychiatry: Suicide/suicidal thoughts or clinical worsening:* Careful monitoring should be carried out during first weeks of treatment, during dose changes and in patients who have history of suicide-related events prior to treatment; close supervision should accompany drug therapy in particular those at high risk especially in early treatment and following dose changes; Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medicinal product, in patients who experience the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms; increased risk of suicidal behaviour with antidepressants in patients less than 25 years old compared to placebo. *Neuropsychiatric symptoms including mania and bipolar disorder:* Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Caution in patients receiving ECT therapy concomitantly. *Hypersensitivity:* should be discontinued promptly if patients experience hypersensitivity reactions during treatment; *Cardiovascular Disease:* caution in patients with cardiovascular disease due to limited clinical experience. Bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease. Monitor blood pressure especially in patients with pre-existing hypertension; consider discontinuation if a clinically significant increase in blood pressure is observed; Concomitant use with a nicotine transdermal system may result in elevations of blood pressure. *Other:* Treatment with antidepressants is associated with increased risk of suicidal thinking and behaviour in children & adolescents with major depressive disorder and other psychiatric disorders. Use with caution in patients with mild to moderate hepatic impairment. Patients with renal impairment should be closely monitored. Older people: Greater sensitivity in some older individuals cannot be ruled out. Bupropion interferes with the assay used in some rapid urine drug screens which can result in false positive readings. WELLBUTRIN XR is intended for oral use only. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* should not be used during pregnancy unless clinical condition requires treatment with bupropion and alternative treatments are not an option. *Lactation:* Bupropion and its metabolites are excreted in human breast milk. Fertility: no data on effect on human fertility. **UNDESIRABLE EFFECTS:** *Very Common* (≥1/10): Insomnia; headache; dry mouth; gastrointestinal disturbance including nausea and vomiting; *Common* (≥1/100, <1/10): Hypersensitivity reactions such as urticaria; anorexia; agitation, anxiety; tremor, dizziness, taste disorders; visual disturbance; tinnitus; increased blood pressure (sometimes severe), flushing; abdominal pain, constipation; rash, pruritus, sweating; fever, chest pain and asthenia. *Refer to the SPC for a full list of undesirable effects.* **LOCAL PRESENTATIONS:** 150mg (x30 tablets); 300mg (x30 tablets). **MARKETING AUTHORISATION NUMBER:** MA192/02301-2. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** January 2019.
For the latest product information, please refer to the full SPC available from: gskpro.com/en-mt/products or contact us at GSK Malta (phone: +35621238131).

REPORTING ADVERSE EVENTS (AEs):
Suspected adverse events should be reported to GSK Malta through: **gskpro.com/en-mt** (Phone: +356212381311, Address: GSK Malta, 1 (1st floor), de la Cruz Avenue, Qormi, Malta). Cases may also be reported through www.medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

Job No: PM-MT-BPR-ADVR-190002
Prepared: April 2019

References:
* **MDD:** Major Depressive Disorder; **SSRI:** Selective Serotonin Reuptake Inhibitor; Post-hoc analysis of subjects with remitted MDD on data pooled from six double blind, randomized trials comparing ≤ 300mg/day bupropion (n=169) with SSRIs (Sertraline, Paroxetine or Escitalopram) (n=324).
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Female Infertility: Causes and Management

Mr Max Dingli
Obstetrician and Gynaecologist

This e-Learning session provides an overview of infertility with focus on female infertility; including its possible causes, required investigations and available treatment options.

LEARNING OBJECTIVES

- To update healthcare professionals' knowledge on the main causes of infertility; with specific focus on the female causes of infertility.
- To provide an overview of the various investigations as well as treatment options which are available and necessary in the management of female infertility.
- To highlight the main indications, complications as well as the main steps of In Vitro Fertilisation (IVF)
- To give an overview of the setup and functions of the Assisted Reproductive Technology (ART) Clinic at Mater Dei Hospital.

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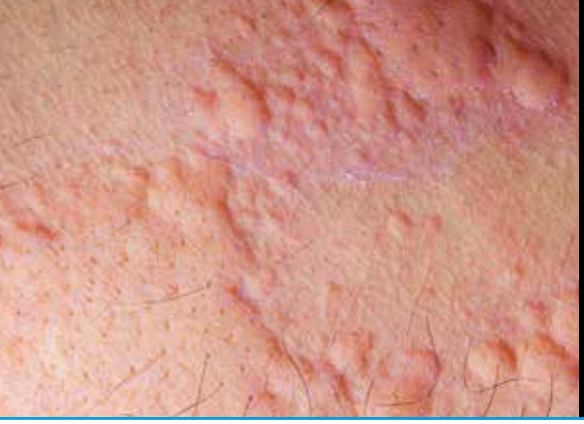

Management of Urticaria: A Practical Approach

Dr Susan Aquilina
Consultant Dermatologist

Urticaria can be diagnosed on the basis of the clinical presentation. While acute urticaria has an identifiable trigger in about 50% of cases, chronic urticaria (urticaria which lasts for longer than 6 weeks) frustratingly tends to remain idiopathic, with 30–40% of patients appearing to have an autoimmune aetiology.

Some patients have a physical cause for their urticaria. A good history and examination are crucial when trying to identify possible urticaria triggers and undirected laboratory investigations are typically fruitless. While non-sedating H1 receptor antagonist antihistamines represent the first-line therapy for urticaria, other treatment options in severe cases include ciclosporin, omalizumab and short courses of oral corticosteroids.

This e-learning session provides an overview of urticaria including the different types of urticaria, causes and treatment options.

LEARNING OBJECTIVES

- To aid healthcare professionals in making a confident clinical diagnosis of urticaria
- To increase knowledge and awareness of the different types of urticaria and of its commonest causes and triggers
- To increase appreciation of the importance of taking a good history in patients presenting with urticaria rather than performing blind laboratory tests and of which laboratory tests may be useful
- To present an update of treatment options for the management of urticaria

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CHRONIC PAIN

PROF. ALBERT CILIA-VINCENTI

TWO TESTED NATURAL COMPOUNDS MAY BREAK PAIN CYCLE COULD THEY BE USEFUL IN NEURODEGENERATIVE DISEASE?

Chronic pain is a substantial medical concern because it is common, can be debilitating, and pain medications may be more dangerous than originally thought.

Analgesic drugs taken for even a few days are now claimed to increase myocardial infarction risk by 48%, using ibuprofen, and by 53% when using naproxen.[1] Chronic use of NSAIDs like ibuprofen is claimed to increase kidney function impairment by 32%.[2] Furthermore, the current opioid epidemic in the US is said to claim over 100 overdose deaths daily.

The challenge in pain control is both addressing the cause of the pain and switching off the pain signal. Is there a safe alternative? Two natural compounds are claimed to work together to reduce the underlying causes of pain. The first compound, **palmitoylethanolamide** (**PEA**), is an anti-inflammatory fatty acid derivative produced by the body in response to inflammation-inducing damage;[3] it acts at the site of tenderness, turning off the pain signal.[4,5] The second, **honokiol**, a Magnolia tree extract, modulates pain perception in the brain. These two compounds are claimed not to cause dependence because they do not act via opioid receptors.

The nature of PEA was first identified by Nobel Laureate Rita Levi-Montalcini, the co-discoverer of the nerve growth factor and the pain signal development and transmission mechanisms.[6-8] PEA is said to be an endocannabinoid, a natural neurochemical signalling molecule which does not bind to specific cannabinoid receptors, and which has no documented risk of dependency or adverse effects. This distinguishes it from most other chronic pain treatments.[9]

Several studies have established PEA as a powerful, peripherally-acting pain reliever.[4,5] One study was conducted on 636 sciatic pain sufferers randomly assigned to placebo or one of two doses of PEA (300mg or 600mg daily). After 3 weeks, both pain reduction and quality–of-life scores were significantly better than placebo, and the larger dose had better outcomes.[10,11]

In pain studies, determination of how many patients would need to be treated to achieve a 50% pain reduction is called the "number needed to treat". The standard number to treat for a useful pain intervention is less than 5, with 1 being statistically perfect (every treated patient achieves at least 50% pain reduction).

In this PEA study, the number needed to treat in the 600mg daily group was just under 3 at week 2 and only 1.5 at week 3.[10,12] A number needed to treat as low as 1.5 is virtually unknown in pain reduction, indicating such a high level of effectiveness which surpasses most pharmaceutical standards.

In another PEA study with carpal tunnel syndrome, subjects were randomly assigned to three groups, placebo, 600mg and 1,200mg daily for 30 days.[13] Nerve conduction measurements at the start and end of the study showed that PEA had slowed median nerve conduction. A faster nerve conduction indicates pain signals are being generated at the sore site. Therefore, this study indicated that PEA recipients' nerve conduction improvements matched their reduced symptoms compared to controls.

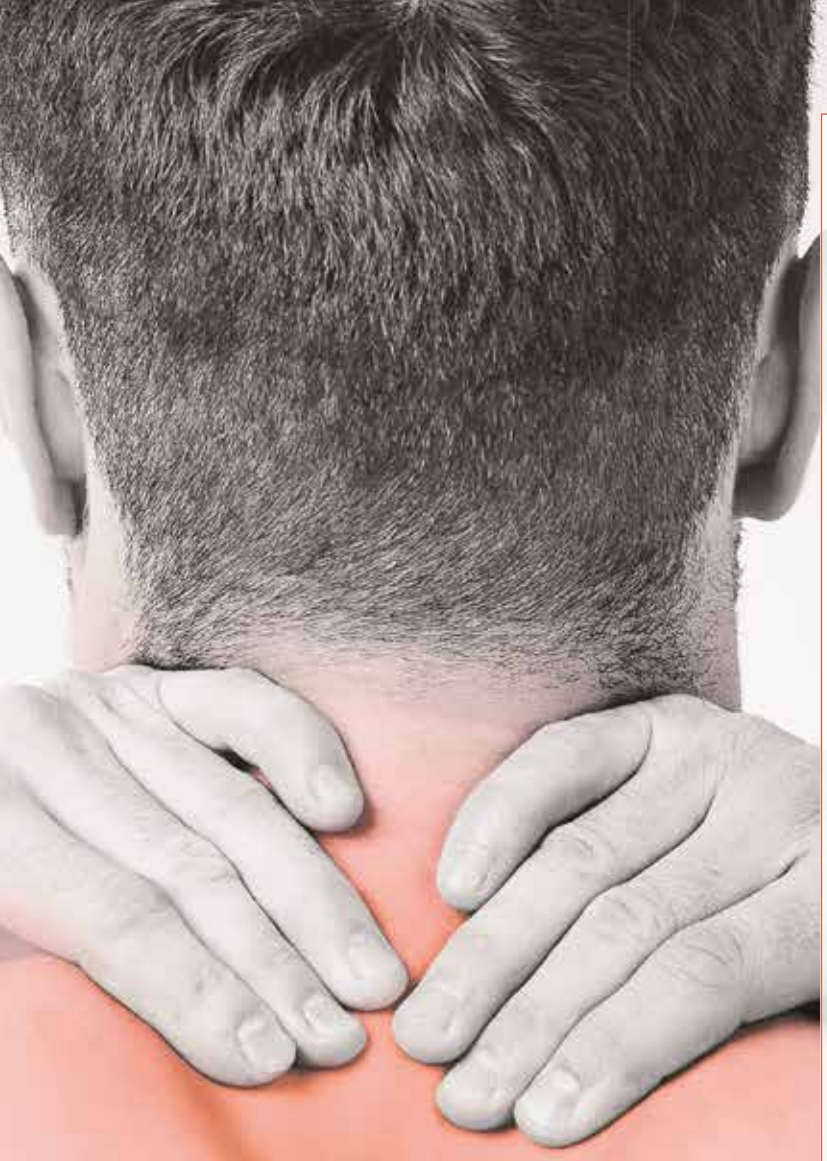
In a study on patients with temporomandibular joint pain, subjects were randomly assigned to 600mg ibuprofen 3 times daily for 2 weeks or 300mg PEA twice daily for 2 weeks. The PEA group experienced significantly greater decrease in pain.[14]

Another study showed that mice treated with morphine plus PEA were less prone to develop morphine tolerance compared with animals on morphine alone.[15] This suggests that PEA combined with an opioid could decrease the risk of tolerance and addiction.

Honokiol has been identified as the second compound that could approach pain reduction from a different aspect to provide deeper, complementary, more consistent relief. It operates in the central nervous system to affect how pain is perceived. It binds to GABA receptors, GABA being a neurotransmitter inducing calming, pain-dampening signals.[16,17]

Loss of GABA receptors and reduced GABA signalling is involved in the transition from acute to chronic pain, leaving the CNS exposed to continued stimulus from an old injury.[18-20] Honokiol mimicks GABA actions, interfering with the chronic pain cycle by restoring a central natural pain-dampening effect. This is being followed up by pharmaceutical companies.[21] Oral honokiol is quickly absorbed and distributed throughout the brain.[22-24]

An animal study has shown how capable honokiol is in its CNS pain-relieving action. Mice were injected with a variety of substances known to activate hyperalgesia receptors.[25] Then they were treated with either honokiol or a control injection.



For each pain-inducing substance the mice were timed on how long they spent licking the painful site, longer licking meaning more severe pain perception. They were then timed on how long they took to withdraw their paw from a hot water bath. In each case, the honokiol-treated animals showed significant reductions in licking time, and significant increases in paw withdrawal time from the hot bath. These actions indicated a reduction in pain and demonstrated how honokiol can help break the chronic pain cycle.

By inference, a honokiol-PEA combination could provide a complementary dual action approach to chronic pain, without the risks seen with conventional analgesic drugs.

Chronic inflammation in the CNS may be involved in the pathogenesis of neurodegenerative conditions such as Parkinson's and Alzheimer's diseases. In a study of 30 advanced Parkinson's patients being treated with levodopa, a cognitive test battery before and after receiving 1,200mg PEA daily for three months and 600mg daily for the rest of the year, found a significant and progressive reduction in both motor and non-motor symptoms.[26] PEA appears to have potential for some reversal of symptoms of chronic neurodegenerative diseases.

PEA is available in Europe under the trade name Normast®. A PEA-Honokiol combination product is marketed as ComfortMAX™ by *Life Extension Europe*, the European division of *Life Extension*, an American food supplement company.

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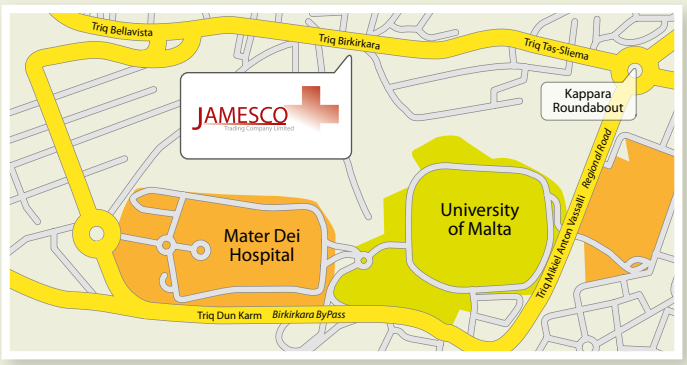

LULLABY OF *BROMO-DRAGONFLY*

DR MICHELLE MUSCAT

Bromo-Dragonfly, also called bromo-benzodifuranil-isopropylamine, is a psychedelic designer drug synthesized by Matthew A. Parker in the laboratory of David E. Nichols at Purdue University in 1998. This drug was first synthesized as a new research probe to investigate central nervous system serotonin receptor structure and activity. Although it was not originally intended for human consumption, it has subsequently been used for recreational purposes.[1] It is a powerful 5-HT2A receptor agonist. This benzodifuran derivative is a strong hallucinogen,[2] similar to LSD but with prolonged duration of action and possible intense hallucination visuals. Heterogeneous effects amongst individuals may be experienced even with the same dose. Overall it is said to be a third as potent as LSD on a weight for weight basis. The drug inhibits monoamine oxidase A.[3]

The name of this compound comes from the fact that its chemical structure is said to resemble a dragonfly. The R stereoisomer is the stronger compound. Bromo-Dragonfly misuse potential is high.[4] Overdoses have potential for toxicity and lethality.[5] It is a strong vasoconstrictor and this effect can lead to limb necrosis. Psychoactive drug poisonings have also been described.[6,7] A case report by Nielsen et al. describes the development of acute psychosis,[8] whilst Wood et al. have reported delayed-onset seizures when the drug was taken in combination with ketamine and cannabis.[9]

Drug formulations include powder, pills, and it may also be sold as impregnated blotter sheets.

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CARPOMETACARPAL OSTEOARTHRITIS OF THE THUMB

MR ALISTAIR PACE

INTRODUCTION

Osteoarthritis of the trapeziometacarpal joint is the second most common site of degenerative joint disease in the hand and mostly affects postmenopausal women and manual workers. The reported radiographic prevalence of the condition is 7% in males and 15% in females. Studies reveal that 33% of women over 40 years of age will have some Xray changes.

To achieve a high degree of prehensile and manipulative function this highly mobile joint is constrained by both the biconcave saddle morphology of the trapezium and the ligamentous constraints.

It is theorized that attenuation of the anterior oblique ligament or beak ligament leads to instability, subluxation and eventually arthritis of the CMC (carpometacarpal) joint. The condition can cause pain, weakness, deformity and loss of function of the thumb and can be very debilitating.[1]

SYMPTOMS AND SIGNS

The symptoms vary in severity and usually progress over time. Patients usually present with swelling at the base of the thumb as well as aching, discomfort and tenderness.

They report a limited range of movement and stiffness as well as loss of strength. Typically they complain of pain with rotatory movements of the thumb in particular opening jam jars or taps. On examination there may be squaring of the base of the thumb due to subluxation of the CMC joint of the thumb particularly in advanced cases. There may also be wasting of the thenar eminence particularly the APB (abductor pollicis brevis) due to stiffness.

Furthermore there may be compensatory hyperextension of the MCP (metacarpophalangeal) joint of the thumb. Movements of the thumb are usually limited and associated with crepitus. There may be a positive axial loading grinding test. If there is associated arthritis in the STT (scapho-trapezio-trapezoid) joint then there will be pain on radial deviation of the wrist. In 50% of cases there may be concomitant carpal tunnel syndrome.

RADIOLOGY

The optimal view requires the Xray beam to be centred on the trapezium and metacarpal with the thumb flat on the cassette and thumb hyperpronated. The conditions present with narrowing of the CMC joint of the thumb, osteophytes, sclerosis and subluxation. (Figure 1)

The clinical signs do not correlate with radiographic findings. In fact whilst symptomatic hand osteoarthritis affects approximately 25% of adult subjects, radiographic changes can be found in up to two thirds of females and half of males older than 55 years of age. The most widely used classification system for the radiographic staging of thumb CMC osteoarthritis is the Eaton and Littler classification ranging from mild (stages 1 and 2) to severe (stage 4) disease associated with pan-trapezial arthritis.[1]

TREATMENT

In the early stages the condition can be satisfactorily treated with NSAIDS, thumb strengthening exercises of the thenar eminence, modification of activities and splinting or bracing of the thumb e.g. a thumb wrap. A variety of injections including steroid injections, hyaluronic acid intra-articular injections and PRP (platelet-rich plasma) injections have been trailed.

A prospective randomized double blind controlled clinical trial comparing PRP and corticosteroid injections confirmed that corticosteroids offer short term relief of symptoms but PrP might achieve a lasting effect of up to 12 months in the treatment of early to moderate TMJ (temporomandibular) arthritis.[2] Moreover hyaluronic acid injections show no difference for the relief of pain and improvement in function when compared to placebo and corticosteroids.[3]

Surgical treatment remains the most effective treatment for this condition. This would entail a trapeziectomy or excision arthroplasty of the base of thumb. In patients where there is associated STT joint arthritis, the procedure may be accompanied by a partial trapezoidectomy through the same incision.

Figure 1. Radiographic feature of base-of-thumb arthritis

A study by Yeoman *et al.* in 2019 has concluded that there is a significant and sustained improvement in patient-reported function after simple trapeziectomy when patients were scored with QuickDASH and EuroQol questionnaires.[4]

The trapeziectomy may be combined with a ligament reconstruction and tendon interposition where a section of FCR (flexor carpi radialis) or APL (abductor pollicis longus) tendon is weaved into the excision arthroplasty after the trapeziectomy to suspend the thumb metacarpal in the void created. Occasionally a temporary k- wire is also inserted to provide further support.[5,6] However the randomized double blind controlled study by Pace *et al.* comparing the 2 groups (trapeziectomy vs trapeziectomy and ligament reconstruction, interposition and k-wire) in 2009 concluded that the DASH scores and PEM (Patient Evaluation Measure) scores were reduced in both groups as did the key and tip thumb pinch but there was no significant difference between the 2 groups at either 3 or 12 months.[7]

In younger patients particularly manual workers a fusion of the CMC joint of the thumb may be considered as opposed to an excision. This is aimed at preserving grip strength. Although this procedure provides good pain relief, stability and length preservation, there is an associated decreased range of movement, inability to put hand down flat and a non-union rate of 12% and increased risk of predisposing adjacent joints to arthrosis.[8]

Prosthetic replacements of small joints are fraught with risks and complications and the same may be applied to arthroplasty of the thumb CMC joint and are thus not a popular choice of treatment. Some studies reveal a 40% risk of instability and dislocation.

Base of thumb arthritis is a common condition and can be debilitating to the function of the thumb and hand. Whilst most patients may be treated non-operatively, various different surgical procedures may be used with varying results.

SUMMARY

- Basal thumb arthritis is common and may be debilitating.
- Most cases may be treated conservatively.
- Injections have mixed results in patients.
- Trapeziectomy is the gold standard surgical procedure that gives long lasting pain relief and improved function.

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UNFORESEEN CIRCUMSTANCES & POWER PLAY

Dr Ian Ellul meets DR JOSEPH CASSAR, consultant psychiatrist & former Health Minister, to discuss personal life and politics.

YOU WERE BORN IN 1966. ONE MAY SAY THAT YOU HAD FIRSTHAND EXPERIENCE OF THE INITIAL STAGES OF THE EVOLUTION OF PACEVILLE. THERE WAS TIGULLIO, STICKS & VIBES. YOUR ADOLESCENCE ALSO COINCIDED WITH THE INFAMOUS SEX, DRUGS & ROCK AND ROLL ERA, CHARACTERIZED BY THE LIKES OF ROLLING STONES, THE WHO, PINK FLOYD, QUEEN AND LED ZEPPELIN. WHAT DO YOU REMEMBER OF THOSE DAYS?

I cherish my childhood and adolescent days. I attended the government primary school in Rabat and subsequently my secondary schooling at St Aloysius College. I remember serving as altar boy in St Domenic's church, which led to my first trip to the Vatican City. Summers were fun. My grandfather had a summer house in St. Paul's Bay. I spent my days with cousins enjoying the sea. At the time, Mintoff's administration had severed the government's grants to church schools; actually in 1982 the government had issued a legal notice which froze all church school fees. Some church schools were constrained to close. With this backdrop, I have fond memories when my class did a fundraising activity and all 30 students entered into an engineless Skoda.

I attended the New Lyceum Sixth Form. This was due to the 20-point system at the time. If I had chosen to remain at St Aloysius College, I would have automatically lost 20 entry points upon applying for University.

Returning to your question, I used to particularly appreciate Pink Floyd. I also remember going to Tigullio in St Julians and the Galaxy disco in Sliema during the weekends. Savoy cinema in Valletta was also a popular place during my adolescence.

HOW DID YOU FIRST MEET YOUR WIFE, WHICH I BELIEVE SOMEHOW SHARES YOUR PROFESSIONAL FIELD?

I met Anna in 6th form. We were both students in the same sciences class. She is a clinical psychologist. We got married soon after graduating from University. We have been together for over thirty years and shared many adventures. One of our greatest adventures was raising two young kids in the US while we were both studying.

YOU GRADUATED AS MEDICAL DOCTOR IN 1990. WHY DID YOU CHOOSE TO SPECIALISE AS PSYCHIATRIST AT YALE UNIVERSITY?

During the two years of housemanship in Malta, I began to understand that psychiatry was the way forward. Perhaps I was somewhat influenced by the fact that Anna had already graduated in psychology. I had decided to further my studies in the UK but a series of events led me to look into universities within the US. Back then, the US was deemed so far away. I remember catching thirteen planes in one week because of the various interviews held in different states. Anna was pregnant with our youngest at the time. I matched with many centres but chose Medical College of Virginia initially. However, after the first year, I applied to further my residency training at Yale. Yale is one of the top training facilities in Psychiatry. The decision was an emotional roller coaster. Once at Yale, I never looked back. The learning experience, practice and friendships I gained were priceless.

YOUR DAUGHTER FOLLOWED YOUR STEPS IN BECOMING A MEDICAL DOCTOR. WILL SHE ALSO FOLLOW YOU INTO POLITICS?

Indeed, my elder daughter is studying psychiatry. Hands on heart, I always tried to avoid influencing my girls on their career decision. But there you go, even my younger daughter, who is a lawyer, opted to read for a Master in Human Rights at Queen Mary University. Both daughters chose careers which delve, either directly or indirectly, in the psychology of people. I think both myself and Anna have unwillingly influenced both of our girls in their choices.

Returning to your question, the answer is a simple no.

YOU REPRESENTED THE PN DURING THE GENERAL ELECTIONS BETWEEN 2004 AND 2015. IN 2003 YOU CONTESTED THE 11TH DISTRICT WHERE YOU OBTAINED 600 VOTES. YOU WERE THEN CO-OPTED ON 24 MAY 2004 AFTER PROF. JOSEF BONNICI RESIGNED FROM PARLIAMENT FOLLOWING HIS APPOINTMENT AS MEMBER OF THE EUROPEAN COURT OF AUDITORS IN LUXEMBOURG. WHAT MOTIVATED YOU TO ENTER INTO POLITICS? WHAT DID YOUR FAMILY SAY?

I was always involved in politics in its wider sense. As a medical student I was president of the students' association, at Yale I was president of the psychiatry residents' association and also, when

I returned back to Malta I became involved in MAM. It was only natural for me to continue this and become involved in politics on a national level.

My stepping into politics was governed by interesting psychodynamics. My father never wanted me to enter politics. He died in 2002 and a year later I decided to run for the national election.

Anna was also apprehensive about my resolution, drawing from her firsthand experience of the hardships of politics; her uncle was the late Dr Lino Gauci Borda, a family doctor and a long-serving MP on the Nationalist Party's ticket. Nonetheless, she always respected and supported my decisions.

IN 2008 YOU WERE ELECTED FROM ANOTHER DISTRICT, THE 7TH WHERE YOU OBTAINED 4338 VOTES. YOU WERE APPOINTED PARLIAMENTARY SECRETARY FOR HEALTH, AND JUST TWO YEARS LATER YOU WERE PROMOTED TO MINISTER FOR HEALTH. WERE YOU SURPRISED OF YOUR RAPID ASCENT TO A MINISTERIAL ROLE?

Yes, I was. I was co-opted because Prof. Josef Bonnici went to the European Court of Auditors. I then became minister since Mr John Dalli was appointed as European Commission for Health and Consumer Policy. This play of events was totally unexpected and to a great extent took me by surprise. Inevitably it created a stir among colleagues who had more experience and wider involvement in politics.

I am really grateful for being given those opportunities during that time. However, the rapid turn of events gave me no time to reflect on it all. I lived through. I am certainly thankful.

IN 2013 YOU WERE ELECTED FROM THE 7TH DISTRICT WITH 4477 VOTES, BECOMING SPOKESPERSON ON ARTS AND CULTURE. YOU RESIGNED ON 16 NOVEMBER 2015 AND DECIDED TO NOT CONTEST THE 2017 GENERAL ELECTION. IN VIEW OF THE FACT THAT YOU WERE FARING WELL IN THE ELECTIONS WHY THROW IN THE TOWEL?

In 2013 I got elected from two districts in fact. Politics was equally rewarding and disappointing. I believe that the medical profession is geared to always offer assistance and that can be a reason why doctors are exploited in politics.

MALTA HAS EXPERIENCED CHANGES LIKE ANY OTHER COUNTRY. THESE CHANGES WOULD HAVE FILTERED IN EVEN IF WE WERE NOT PART OF THE EU. THE CATALYST FOR THIS HAS BEEN THE SOCIAL MEDIA WHICH DRIVES THE THINKING PROCESS

My mantra never fully fit within partisan politics. Whoever knows me, knows that for me human dignity precedes everything. I will go out of my way to help anyone without expecting anything in return. The political climate today is unfortunately struggling to recall the real values that govern human dignity and the real reasons that should draw us to a political service.

For now, I can tell you I will not set foot in politics again.

YOU MANAGED TO SUCCESSFULLY OVERCOME OBESITY OVER A RELATIVELY SHORT PERIOD OF TIME. WHAT WAS YOUR SECRET?

Yes, that was a very unexpected and unique challenge. It all started some years ago when we went to the bank to take a loan to buy a family home. The bank informed me, that being overweight, I had to pay a higher premium on the health insurance. That was a watershed moment in my life. I started to run for approximately two hours, four times a week. Now I am 70 kg. I started to love running. When I left politics three years ago, I joined a running club. I would recommend it to everyone.

IS EXERCISE THAT IMPORTANT FOR OUR HOLISTIC WELL-BEING?

The WHO recommends 150 minutes of exercise per week. I cannot overemphasize the contribution of exercise towards mental and physical health. The endorphins which are produced are a remarkable experience with an added benefit of stress reduction and mental well-being.

MALTA HAS METAMORPHOSIZED IN RECENT TIMES. WE SAW THE INTRODUCTION OF CIVIL UNIONS FOR SAME-SEX COUPLES AND EMERGENCY CONTRACEPTION AS WELL AS THE DECRIMINALISATION OF THE VILIFICATION OF RELIGION TO NAME A FEW. WHAT ARE YOUR VIEWS ON MALTA: PAST, PRESENT & YET TO COME?

Malta has experienced changes like any other country. These changes would have filtered in even if we were not part of the EU. The catalyst for this has been the social media which drives the thinking process. This is, per se, universal. I am not worried about the things you mentioned. Obviously, I am worried about the looming spectre of abortion. However, I am particularly worried about the upbringing of today's children who spend *excessive* time playing online games. Just as an example, when we were fifteen, we used to talk about and try to reach out to our peers and the opposite gender. Today we are seeing worrying trends … adolescents are opting to spend entire weekends at home playing online games.

Malta has a rich cultural history. Today Malta is transforming. Change is inevitable. Being a nation of resilient and courageous people, my hope is that we find creative ways to keep imparting the true solid values of respect, loyalty, care and honour to future generations. Each one of us has an important role to play in our daily lives in shaping Malta's future.

I READ THE SYNAPSE BECAUSE...

It is readily available since it comes directly in your letter box. It also contains very relevant information. You ought to be proud of your product.

• PART III •

DR PIERRE VASSALLO

ULTRASOUND ASSESSMENT OF RIGHT UPPER QUADRANT ABDOMINAL PAIN

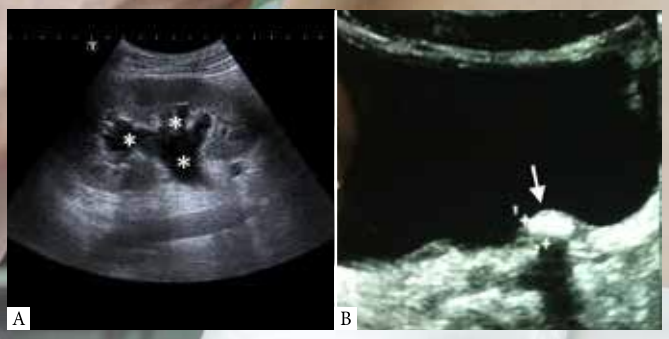

Figure 1a. Longitudinal US scan of the kidney showing a dilated PC system (*). **b.** Transverse US scan of the bladder showing a stone located at the ostium of the right ureter (arrow).

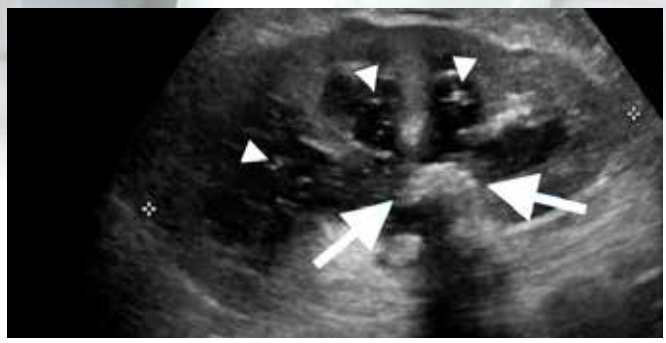

Figure 2. Longitudinal US scan of the kidney showing a dilated PC system that contains a stone (arrows) and debris (arrowheads).

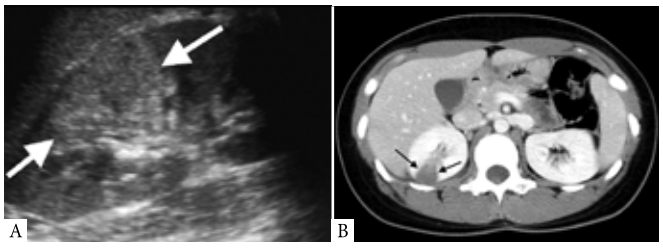

Figure 3a. Longitudinal US scan of the kidney showing at segmental area of hyperechogenicity (arrows) that correlates with focal nephritis. **b.** Contrast-enhanced CT scan showing a segmental area of hypoperfusion (arrows).

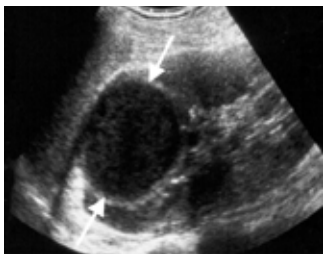

Figure 4. Longitudinal US scan through the upper pole of the kidney showing a well-defined hypoechoic lesion (arrows) that represents a renal abscess.

Parts 1 and 2 of this article discussed the importance of having an efficient diagnostic algorithm for right upper quadrant (RUQ) abdominal pain, since it is one of the most common presenting complaints to any clinic or emergency department. While acute cholecystitis is the most frequent cause of RUQ pain, more than a third of cases are due to other conditions. The said articles also showed that abdominal ultrasound is the imaging modality of choice because it is easily accessible, rapid, cost-effective, and safe since it involves no ionising radiation or potentially nephrotoxic intravenous contrast agent.[1] Abdominal US visualises multiple upper abdominal organ systems that could be the source of the patient's pain.

Parts 1 and 2 of this article described the US findings related to the biliary, hepatic, pancreatic and gastrointestinal causes of RUQ pain, while this final Part 3 will deal with renal, adrenal, thoracic and vascular causes.

RENAL CAUSES OF RUQ PAIN

Upper urinary tract obstruction by stones is a common cause of right upper abdominal pain; classically this is described as pain radiating from the loin to the groin on the side of obstruction. Renal obstruction is readily diagnosed on ultrasound by the presence of hydronephrosis (Fig 1a). A search for the obstructing stone often finds it located at the junction between the renal pelvis and the ureter or at the point of entry of the ureter into the bladder (Fig 1b). Stones located in between these levels are rarely visible on ultrasound and are best localised and measured on non-contrast CT. Location and size of the stone are important parameters since they determine whether a stone may pass spontaneously or require surgical intervention.

Infection in the right upper urinary tract may present with acute RUQ pain; more typically, it presents with flank pain, fever, rigors and dysuria. The most common form of upper urinary tract infection is bacterial pyelonephritis, which is most frequently seen in women aged 15 to 40 years. Bacterial pyelonephritis consists of infection in the ureter and pelvicalyceal system that extends into the renal parenchyma and is usually due to ascending infection from the bladder. This may occur even in the absence of vesico-ureteric reflux and is thought to be due to functional obstruction resulting from bacterial endotoxins that inhibit ureteric peristalsis. While US cannot distinguish a sterile upper urinary tract obstruction from a dilated ureter and pelvicalyceal system

due to pyelonephritis, debris within the distended pelvicalyceal system may be seen in the latter case (Fig 2). The nephritis aspect of pyelonephritis is often occult on US but may appear as a segmental area of increased echogenicity (Fig 3a). On contrast-enhanced CT, nephritis presents as an area of hypoperfusion (Fig 3b). Pyonephrosis and renal abscess formation (Fig 4) are potential complications of pyelonephritis that may occur in the absence of timely percutaneous drainage of the infected collecting system and antibiotic therapy.

Spontaneous haemorrhage into a renal cyst or neoplasm may present with RUQ pain. The most common tumours to present with spontaneous haemorrhage are angiomyolipomas particularly if they are over 4cm in diameter (Fig 5). Less commonly, haemorrhage may be seen in renal adenocarcinomas. Occasionally, haemorrhage may obscure the causative lesion on imaging. Repeat imaging with US, CT and/or MRI after resolution of the haemorrhage may be required to identify the cause.

ADRENAL CAUSES OF RUQ PAIN

The adrenal gland is rarely a source of RUQ pain. The main adrenal condition that leads to pain is intraglandular haemorrhage. When symptoms are present, they may include flank pain and low grade fever. Symptoms of adrenal insufficiency would only occur with bilateral adrenal involvement and when more than 90% of adrenal tissue is destroyed. Spontaneous adrenal haemorrhage is seen in conditions of stress (surgery, severe burns and sepsis), pregnancy, bleeding diatheses and with anticoagulant therapy.[2] Benign and malignant tumours of the adrenal gland may also undergo haemorrhage, which may require serial imaging follow-up to identify the causative lesion. Only large adrenal haematomas are visible on ultrasound (Fig 6). Smaller ones are only visible on CT or MRI. Intraglandular haemorrhage initially appears as a solid mass, which later shows central fluid consistency and may proceed to develop rim calcification. Once intraglandular haemorrhage has resolved, a residual cyst or dystrophic calcifications may persist within the gland.

THORACIC CAUSES OF RUQ PAIN

Any condition that results in right basal pleuritis can result in RUQ pain. These conditions include a right lower lobe pneumonia, pleural effusion, pulmonary infarction (pulmonary embolism) and pulmonary/chest wall neoplasms. An abscess originating in the lung from pneumonia or in the liver (e.g. amoebic abscess) may cross through the diaphragm. If peripherally located near the chest wall, these conditions may be detected by ultrasound (Fig 7). However, CT is the most reliable tool for evaluating the organs on either side of the diaphragm.

Chest wall tumours are mostly metastatic lesions originating from other organs. However, primary chest wall tumours such as lymphomas or sarcomas are also seen in clinical practice. While CT and MRI may help identify the primary lesion in the case of metastatic disease, US is very useful for confirming the presence of a chest wall mass and for guiding biopsy particularly in case of an unknown primary tumour.

VASCULAR CAUSES FOR RUQ PAIN

Thrombosis of the hepatic veins, portal veins and hepatic arteries may present with RUQ pain. These three entities can be distinguished from one another with US.

Hepatic artery thrombosis is the most common complication of liver transplantation. It may however also occur due to tumour infiltration, hypercoagulability disorders, vasculitis (e.g. systemic lupus erythematosus), eclampsia and as a complication of surgery. Due to its dual blood supply (hepatic artery and portal vein), the liver is relatively resistant to hepatic infarction or ischaemic hepatitis. An altered hepatic arterial flow pattern on spectral and colour Doppler US may be noted with altered, diminished or absent flow (Fig 8). In the transplanted liver, hepatic arterial

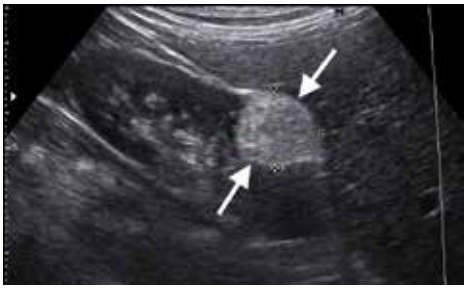

Figure 5. Longitudinal US scan through the kidney showing a well-defined hyperechoic mass (arrows) in the anterior portion of the lower renal pole, a typical appearance of an angiomyolipoma.

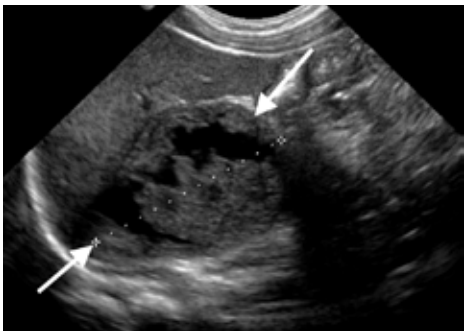

Figure 6. Longitudinal US scan through an enlarged heterogeneous right adrenal gland (arrows); the altered size and texture are due to spontaneous intraglandular haemorrhage that occurred during pregnancy.

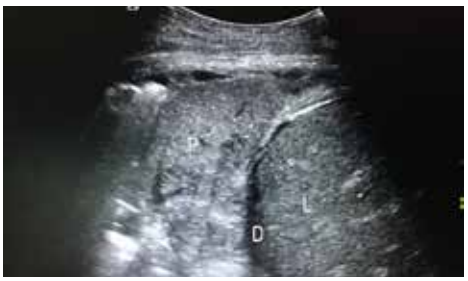

Figure 7. Intercostal US scan showing consolidation in the right lung base due to pneumonia (P) and the adjacent diaphragm (D) and liver (L).

Figure 8a. Spectral Doppler US through the main hepatic artery shows low peak systolic flow velocity and a high resistive index proximal to the occlusion. **b.** Spectral Doppler US distal to the occlusion in the left main hepatic artery shows diminished flow and a relatively flat waveform.

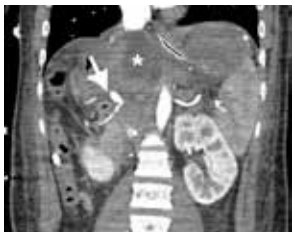

Figure 9. CT angiogram showing main hepatic arterial occlusion (arrow) in a transplanted liver with areas of liver infarction (*).

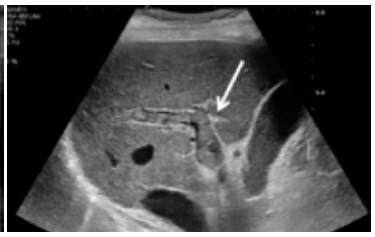

Figure 10. Longitudinal US scan through the main portal vein showing echogenic thrombus filling the said vein (arrow).

occlusion has more severe consequences; contrast-enhanced US or CT angiography (Fig 9) are required to assess the extent of arterial occlusion and of transplant infarction.

Portal vein thrombosis may be asymptomatic; however, it may present with RUQ or diffuse abdominal pain particularly if associated with mesenteric vein thrombosis. Portal vein thrombosis may be due to benign causes or due to an infiltrating tumour from adjacent organs. The distinction is important as the treatments and prognoses for both conditions differ. Benign (or bland) portal venous thrombosis may be due to a hypercoagulability state, inflammatory conditions including vasculitis, inflammation of adjacent organs (pancreas, bowel, biliary tree), use of the oral contraceptive pill and pregnancy. Superior mesenteric vein thrombosis has also been observed in high intensity athletes wearing tight running clothing and experiencing dehydrated states. The pain experienced in portal vein thrombosis is mainly due to bowel ischaemia, which may progress to bowel infarction. The thrombus in the portal vein is seen as a filling defect on US (Fig 10) and diminished monophasic flow with normal flow direction (hepatopetal) may be evident on spectral Doppler US in the case of incomplete portal venous occlusion.

Malignant portal vein thrombosis is most commonly due to invading hepatocellular carcinoma, which is itself more common in the presence of hepatic cirrhosis. Tumor thrombus in the portal vein may also arise from pancreatic carcinoma, cholangiocarcinoma and metastatic disease. One possibility to distinguish bland from tumour thrombus in the portal vein is to identify its continuity with the adjacent tumour in the latter case. Another feature is the presence of vascularity within the thrombus in the case of tumour thrombus (Fig 11), while bland thrombus is avascular.

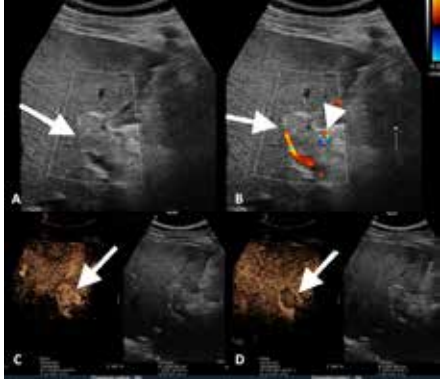

Figure 11a. Longitudinal US scan through the portal vein showing tumour thrombus (arrow). **b.** Colour Doppler US scan through the thrombosed portal vein (arrow) showing vascularity within the thrombus (arrowhead). **c.** Contrast-enhanced US showing early (arterial phase) enhancement within the tumour thrombus (arrow). **d.** Delayed-phase contrast-enhanced US showing washout of contrast within the thrombus (arrow).

Cavernous transformation of the porta hepatis is a consequence of portal vein thrombosis; it is usually evident on colour Doppler US with absent portal vein flow and numerous surrounding tortuous collateral vessels (Fig 12).

Hepatic vein thrombosis is more commonly primary (75% of cases) due to a venous condition such as thrombosis, stenosis or web formation; it is classified as secondary (25% of cases) when it is due to extrinsic tumour compression. The clinical picture is usually of Budd Chiari Syndrome (BCS), which consists of the clinical triad of RUQ pain, hepatomegaly and ascites. US is the imaging modality of choice showing hepatomegaly (particularly caudate lobe enlargement), a coarsened liver texture, absent hepatic veins with collateral hepatic veins, a compressed inferior vena cava, splenomegaly and ascites (Fig 13). Absence or reversed flow may be noted in the hepatic veins, and identification of collaterals draining into the subcapsular and intercostal veins are highly specific signs of BCS.

CONCLUSION

This three-part article clearly presents the complexity of the right upper abdominal quadrant due to the presence of numerous organs each providing its own spectrum of disease. US is a rapid and efficient exam that not only guides further diagnosis and management but often alone provides detailed and specific diagnoses. To harvest the full potential of US in the diagnosis of RUQ pain one requires a sonographer with considerable experience as well as a detailed knowledge of the possible aetiologies and sonographic findings related to all the disease entities described above. A subtle or even equivocal US finding can prompt further evaluation with more complex imaging modalities such as CT or MR and could expedite the diagnostic process.

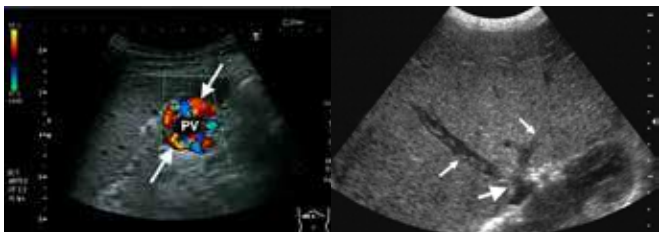

Figure 12. US scan through the portal vein showing no flow centrally within the portal vein (pv) and numerous tortuous collateral vessels around the portal vein (arrows).

Figure 13. Transverse US scan through the liver showing thrombus in the hepatic veins (small arrows) and stenosis of the inferior vena cava (larger arrow).

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1. American College of Radiology. ACR Appropriateness Criteria: right upper quadrant pain. https://acsearch.acr.org/docs/69474/Narrative/. Published 1996. Updated 2013. Last review date: 2013. Accessed January 26, 2018.
2. Jordan E, Poder L, Courtier J, et al. Imaging of nontraumatic adrenal hemorrhage. AJR Am J Roentgenol 2012;199(1):W91–W98.

SEROXAT

The Anxiolytic Antidepressant:[1,2]

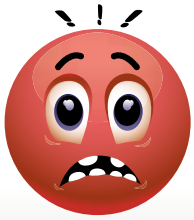
Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]



Panic Disorder[3]

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

SEROXAT ABRIDGED PRESCRIBING INFORMATION *Please refer to full Summary of Product Characteristics (SPC) before prescribing.*

TRADE NAME: SEROXAT. **ACTIVE INGREDIENT:** Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20 mg. **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:** 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 40 mg 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:** Treatment should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment 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: patients should be closely monitored; Use of paroxetine has been associated with development of akathisia: most likely to occur within first few weeks of treatment: do not increase dose in these patients; Serotonin syndrome/ neuroleptic malignant syndrome may develop rarely: treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. Do not use in combination with serotonin-precursors; Use with caution in patients with a history of mania, severe renal and hepatic impairment, diabetes (there have been studies suggesting an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered) and in epilepsy; Drug should be discontinued if patients who develop seizures; There is little clinical experience of concurrent use with ECT; Use with caution in narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia; Caution when administered concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase risk of bleeding; 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. *Refer to full SPC for information on drug interactions.* **PREGNANCY/ FERTILITY/LACTATION:** ***Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated due to potential increased risk of cardiovascular malformations during the first trimester; symptoms such as respiratory distress, cyanosis, apnoea, seizures and other complications may occur in the neonate after maternal paroxetine use in later stages of pregnancy and increased risk of persistent pulmonary hypertension of the newborn (PPHN). ***Lactation:*** Use during lactation can be considered. **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, impaired concentration, blurred vision, yawning, constipation, diarrhoea, 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, headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility were observed. *Refer to full SPC for the full list of adverse reactions.* **LOCAL PRESENTATIONS:** 20 mg Tablets (by 30 tablets). **MARKETING AUTHORISATION HOLDER:** SmithKline Beecham Ltd. **MARKETING AUTHORISATION NUMBERS:** MA172/00201. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** July 2017.

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

REPORTING ADVERSE EVENTS (AEs):

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

Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

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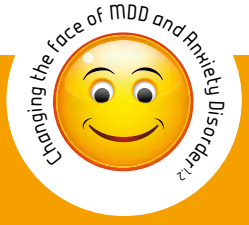

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