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- Vitamin D: its role in the musculoskeletal system and beyond
- Meeting Prof. Everaldo Attard

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

‡ Primary end point.

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

ENTRESTO™▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥ 100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Frimley Business Park, Camberley, GU167SR, United Kingdom. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2016-MT-ENT-16-JUN-2016

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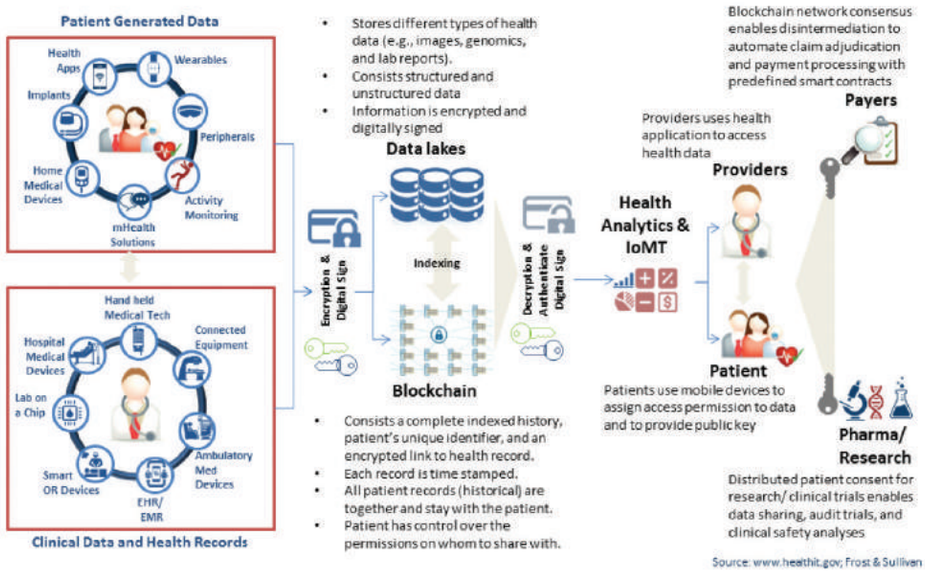
EDITORIAL

BLOCKCHAIN & HEALTHCARE
WILL THERE BE OFFSPRING?

Blockchain technology was invented in 2009 as platform for cryptocurrencies (most of us are familiar with bitcoin). In essence, it is a generic tool to keep secure data in a decentralized encrypted ledger of transactions across a peer-to-peer network. With this network, participants may confirm transactions without the need for a centralized certifying body. So there is one shared secure ledger which is spread across a network of synchronized, replicated databases which are visible to anyone with access to the system.

Every time a digital transaction occurs, it is encrypted in a 'block' with other transactions happening at the same time, hence its name. Taking the fintech industry as example, these transactions would consist of buying and selling executions. In healthcare, taking hospital electronic records as an example, these 'blocks' would relate to e.g. investigation results such as bloods. These executions are validated, in our case by physicians, having an access key. Then the blockchain software timestamps each validated block and adds it to the existing chain of older blocks, in chronological order. The sequence shows every transaction made in the history of that ledger, whether it be bloods or an arthroscopy [healthcare], or bitcoin sales [fintech].



This technology is also particularly relevant for medication administration records. Let us consider a patient who is taking clopidogrel, paracetamol and simvastatin. Today, each electronic record [where available] is essentially a snapshot; it doesn't necessarily tell the prescriber what the patient is actually taking at a specific moment in time. But with blockchain, each prescription is like a deposit. When a prescriber discontinues a medication, this is like a withdrawal. Using blockchain, there is no need for a prescriber to go through all the 'deposits' and 'withdrawals' - they would just see the real-time 'balance'.

In the next issue, we will discuss even further the interesting applications of blockchain in our field.

Ian Ellul

Cover: Celebrating TheSynapse 21st Birthday

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

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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- ✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

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Mini 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. **PRESENTATIONS:** Supplied in 100 ml glass bottle with a dosing spoon. **INDICATIONS:** Treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae.* **POSOLOGY & ADMINISTRATION:** Oral use; recommended dose of 90/6.4 mg/kg/day in two divided doses. **CONTRAINDICATIONS:** Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. **SPECIAL WARNINGS & PRECAUTIONS:** Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Augmentin ES contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). *Refer to the SPC for full list of precautions.* **INTERACTIONS:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. **PREGNANCY & LACTATION:** Use should be avoided unless considered essential by the physician. **UNDESIRABLE EFFECTS:** Very common (≥ 1/10): diarrhoea. Common (≥ 1/100, < 1/10): mucocutaneous candidosis, nausea, abdominal pain. *Refer to the SPC for full list of undesirable effects.* **AUTHORISATION NUMBER:** AA 1051/00101. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline Bulgaria EOOD. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** May 2016 **In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131) *REPORTING ADVERSE EVENTS (AEs):* If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131) **Alternatively, any suspected AEs and m edication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:** Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

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For more information and dosing instructions:
www.hcp.gsk.com.mt/products/list/augmentin.html

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ISSUE GUIDE

CONGRATULATIONS

Heartful congratulations to all newly qualified doctors, pharmacists, dentists and health-related professions from all the staff at The Synapse.

VITAMIN D

ITS ROLE IN THE MUSCULOSKELETAL SYSTEM AND BEYOND

ROSALIE MAGRO & ANDREW BORG

ABSTRACT

Vitamin D deficiency has a high prevalence due to inadequate exposure to sunlight and its limited presence in foods. Vitamin D deficiency has well-known consequences on the musculoskeletal system, namely osteoporosis and frequent falls in the elderly, in view of its effect on calcium absorption. The discovery of the vitamin D receptor in many cells and its ability to regulate the transcription of over 200 genes, has created interest with regards to the role of vitamin D in the modulation of cell growth, inflammation and immune functions. Guidelines recommend screening individuals at risk of vitamin D deficiency, and supplementing when necessary.

KEYWORDS

Vitamin D, osteomalacia, autoimmune disease, malignancy, cardiovascular disease

VITAMIN D PHYSIOLOGY AND FUNCTION

Vitamin D is a fat-soluble vitamin which is only present in few foods, mainly in oil-rich fish such as salmon, mackerel, and herring. The main source (80-90%) of vitamin D is its synthesis in the skin upon absorption of UVB radiation by 7-dehydrocholesterol.[1] It then undergoes hydroxylation in the liver to 25-hydroxyvitamin D; and then further hydroxylation to 1,25-hydroxyvitamin D by the enzyme 1α-hydroxylase. 1,25-hydroxyvitamin D interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues.[1,2] 1,25-hydroxyvitamin D promotes calcium absorption in the gastrointestinal tract and maintains adequate serum calcium and phosphate concentrations.[3] 1,25-hydroxyvitamin D also acts through its vitamin D receptor (VDR) in the osteoblast to stimulate the expression of receptor activator nuclear factor κB ligand. The latter interacts with the receptor activator of nuclear factor κB to stimulate immature monocytes to become mature osteoclasts, which dissolve the matrix and mobilize calcium and other minerals from the skeleton. It is thus important for bone growth and bone remodelling.[4] In the kidney, 1,25-hydroxyvitamin D stimulates calcium reabsorption from the glomerular filtrate.[1,5] VDR is present in most cells and can regulate the transcription of over 200 genes. It has multiple biological actions, including modulation of cell growth, neuromuscular and immune functions, and reduction of inflammation.[6]

VITAMIN D DEFICIENCY

Vitamin D deficiency has been defined as serum 25-hydroxyvitamin D of less than 20ng/ml; while vitamin D insufficiency is defined as serum 25-hydroxyvitamin D of 21–29ng/ml.[1] Vitamin D deficiency is common; its prevalence in adults in Europe ranges from 34% to 67%.[7] The major cause of vitamin D deficiency is inadequate exposure to sunlight.[8] Vitamin D synthesis in the skin is reduced by more than 95% by using sunscreen with a sun protection factor of 30.[9] People with a naturally dark skin tone are more prone to vitamin D deficiency, since they require at least three to five times longer sun exposure to make the same amount of vitamin D as a person with a white skin tone.[10,11] Other risk factors include obesity, fat malabsorption, and medications including anticonvulsants and anti-retroviral therapy.[12,13]

CONSEQUENCES OF VITAMIN D DEFICIENCY

Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism. Vitamin D deficiency causes a decrease in the intestinal calcium and phosphorus absorption, resulting in an increase in parathyroid hormone levels.[1] Secondary hyperparathyroidism maintains normal serum calcium levels by promoting calcium absorption from bone and increasing phosphorus excretion by the kidneys. The increase in osteoclastic activity creates local foci of bone weakness and a generalized decrease in bone mineral density, resulting in osteopaenia and osteoporosis. The increased phosphorus excretion results in lower serum phosphorus levels, causing a mineralization defect in the skeleton.[14] In young children this results in a variety of skeletal deformities classically known as rickets.[15] In adults, this mineralization defect known as an osteomalacia, often goes undetected. It causes a decrease in bone mineral density and is associated with bone and muscles aches.[16] Vitamin D deficiency also causes muscle weakness; affected children

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[THE PREVALENCE OF VITAMIN D DEFICIENCY] RANGES FROM 34% TO 67% ... GUIDELINES RECOMMEND SCREENING FOR VITAMIN D DEFICIENCY IN PATIENTS AT RISK [INCLUDING] OBESE INDIVIDUALS AND ELDERLY PATIENTS SUFFERING FROM FREQUENT FALLS

have difficulty standing and walking, whereas the elderly have more frequent falls and higher fracture risk.[15,17,18]

The discovery of the presence of VDR and the enzyme 1α-hydroxylase in a large number of different cells has created interest on the importance of VDR-directed gene expression on the function of many tissues. A large number of studies have explored the effects of vitamin D beyond its well-known effects on the musculoskeletal system. Observational studies have described associations between low circulating levels of 25-hydroxyvitamin D and a large number of diseases, including cardiovascular diseases, malignancies, diabetes, obesity and autoimmune diseases.[19-22] Moreover, polymorphisms of VDR have been associated with several autoimmune diseases, such as systemic lupus erythematosus, type 1 diabetes, autoimmune thyroid disease, and with a number of malignancies.[23-29]

DIAGNOSIS OF VITAMIN D DEFICIENCY

Guidelines recommend screening for vitamin D deficiency in patients at risk, such as patients with osteoporosis, chronic kidney disease, liver failure, malabsorption, patients on anticonvulsants, obese individuals and elderly patients suffering from frequent falls.[30] Serum 25-hydroxyvitamin D is the major circulating form of vitamin D, and it is recommended to assess its level in order to evaluate vitamin D status.

TREATMENT OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

The guidelines recommend that adults who are vitamin D deficient are treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily for 8 weeks to achieve a blood level of 25-hydroxyvitamin D above 30ng/ml. This is then followed by maintenance therapy of 1500–2000 IU daily.[30] To treat vitamin D deficiency in obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, such as anti-convulsants, the guidelines recommend a loading and maintenance dose that is two to three times higher. They recommend a loading dose of at least 6000–10,000 IU daily, followed by maintenance therapy of at least 3000–6000 IU daily.

CONCLUSION

Adequate vitamin D is vital for maintaining good bone and muscle health. Observational studies suggest a role of vitamin D in the development of autoimmune diseases, malignancy and cardiovascular disease. Large randomised controlled studies are required to define the role of vitamin D in these conditions. Screening for vitamin D deficiency in individuals at risk is recommended, followed by supplementation in vitamin D deficiency and insufficiency.

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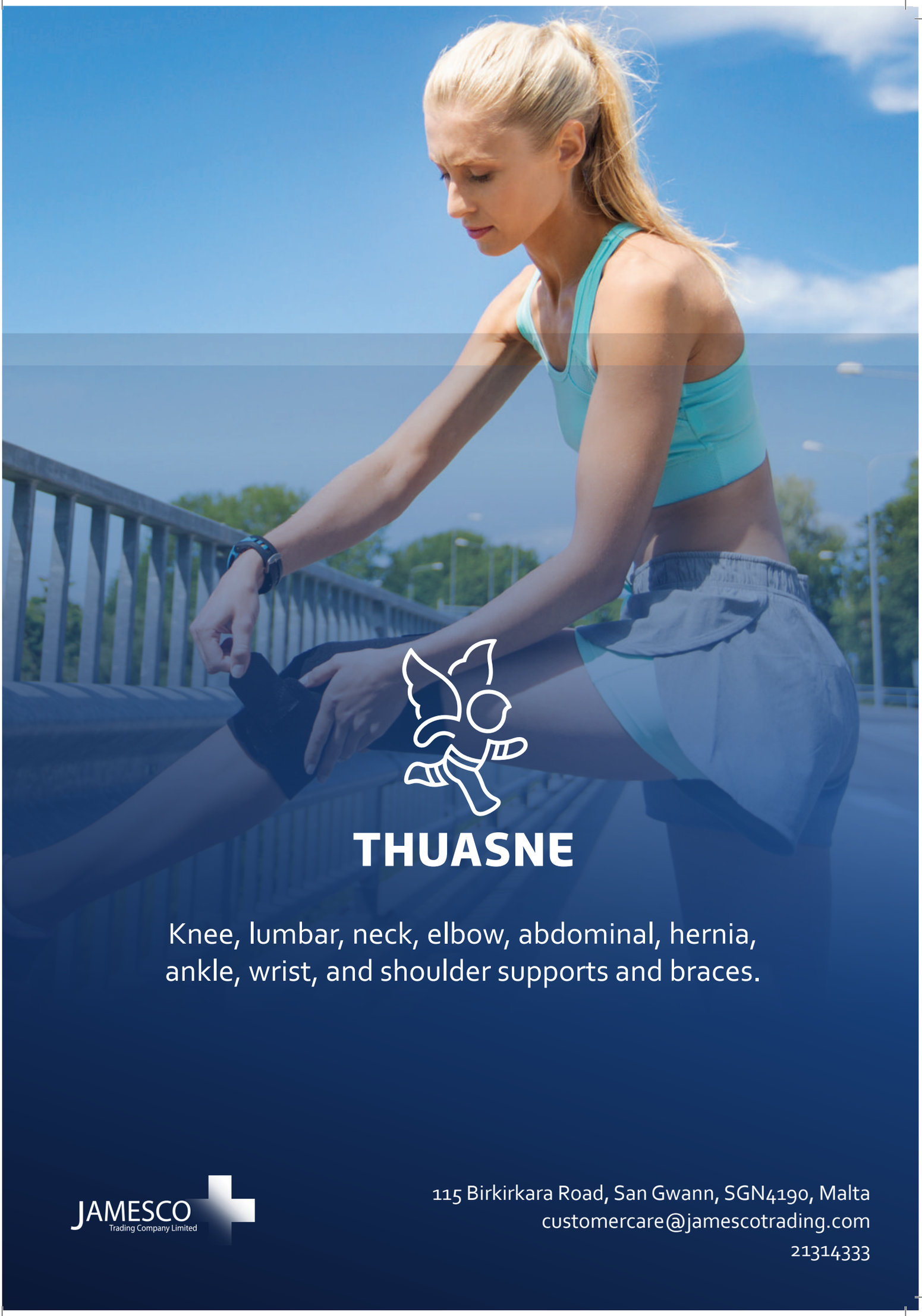

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WITH ULTIBRO® BREEZHALER® EXACERBATION PREVENTION IS IN YOUR HANDS[1]

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

FLAME STUDY RESULTS[1]

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

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

*Fluticasone/salmeterol 500/50 mg BID. †Lung function trough FEV_1 (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] ‡Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] §Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89, P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83, P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87, P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

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

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

Ultibro Breezhaler inhalation powder, hard capsules

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

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

2016-MT-ULT-10-NOV-2016

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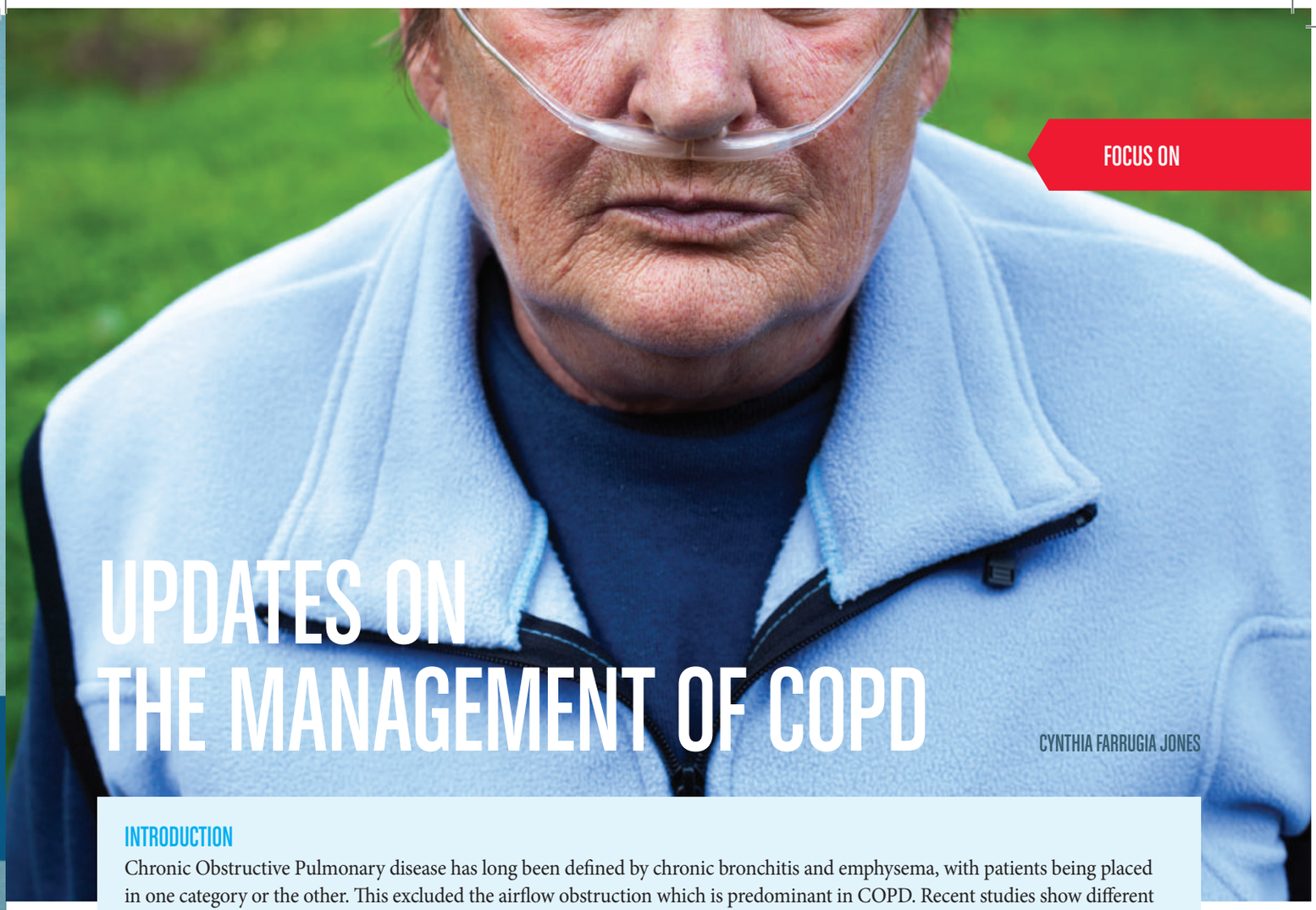


UPDATES ON THE MANAGEMENT OF COPD

CYNTHIA FARRUGIA JONES

INTRODUCTION

Chronic Obstructive Pulmonary disease has long been defined by chronic bronchitis and emphysema, with patients being placed in one category or the other. This excluded the airflow obstruction which is predominant in COPD. Recent studies show different mechanisms of airflow obstruction: [1] loss of support of the small airways in emphysema, [2] chronic inflammation taking part in the smaller airways, and [3] presence of mucus in the small airways.[1] COPD has now a more flexible definition of preventable and treatable disease with airflow limitation that is not fully reversible and an inflammatory response to noxious particles.

UPDATES ON THE MANAGEMENT OF COPD

Smoking still remains the primary culprit but with a more complicated association, since as reported in the literature, only 20-40% of those exposed to cigarette smoke develop COPD.[2,3] Many patients in certain parts of the world have never smoked but have been exposed to wood flame during cooking. Thus, the etiology of COPD includes the effect of harmful agents, genetic predisposition, infectious agents and airway hyper-responsiveness.[4]

Currently COPD is the 6th leading cause of death, but for the year 2020, it is estimated to be ranked third.[5] This is partly being attributed to the gaining popularity of water pipe smoking (Fig. 1) amongst youths in the Middle East.

According to the WHO Study Group on Tobacco Product Regulation, a typical one hour-long session of water pipe smoking involves inhaling 100-200 times the volume of smoke inhaled by one cigarette.

LUNG FUNCTION DECLINE

Fletcher and Peto (Fig. 2) demonstrated that smokers have a more accelerated loss in lung function, which ultimately leads to symptomatic COPD.[6] The loss of lung function is thought to be

Figure 1. A Middle-East water pipe

about 60 ml of forced expiratory volume in 1 second (FEV_1) per year, as compared to the normal loss of lung function, which is about 30 ml per year. This study[6] showed that 15% of smokers are susceptible to COPD.

Recent studies report the proportion of smokers who are susceptible to COPD to be 30-40%. Anthonisen et al. found that people who quit smoking had a small loss of lung function of only 27 ml a year, as compared to those who continued to smoke, who lost about 60 ml per year.[7] Regarding the ones who quit intermittently, the study found their loss of lung function comparable to those who never quit smoking, which means that smoking should be completely discontinued for patients to obtain the full benefit of doing so.

The most recent data is from the ECLIPSE study.[8] The mean decline in lung function in smokers was actually less than expected, averaging approximately 33 ml per year, with only 38% of patients reaching a FEV_1 decline of more than 40 ml per year. The reasons behind this slow decline may be related to environmental conditions or treatment.[8] This data suggests that treatment probably does have a positive impact on the lung function of COPD patients. There is increasing interest in the frequency of COPD exacerbations, since this was found to relate to prevention and treatment. Most of the new drugs being investigated and developed are targeting patients with the 'frequent-exacerbation' phenotype.

The ECLIPSE data, showed that, depending on the overall Global Initiative for Obstructive Lung Disease (GOLD) stage, a significant proportion of patients had 2 or more exacerbations per year, and were thus defined as frequent exacerbators.[9] More than 75% of treated patients in these studies were given long-acting bronchodilators and/or inhaled steroids. The method to identify the frequent exacerbators in clinical practice is their history. Other parameters that are helpful to identify these frequent exacerbators include having a more severe lung function, a worsening quality of life and a high white cell count.

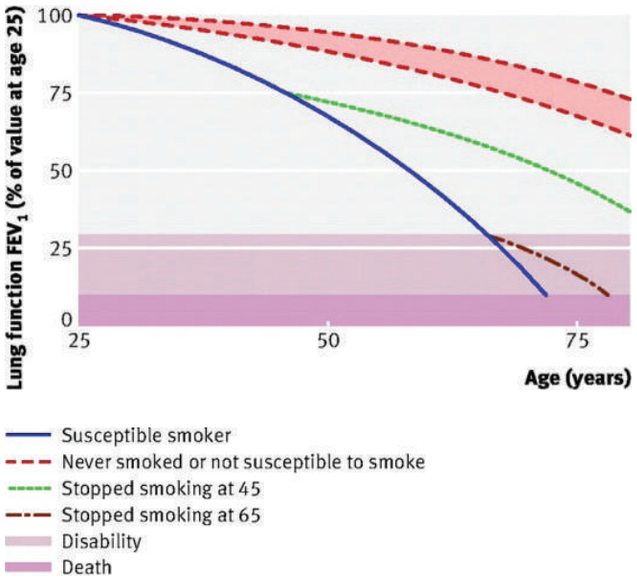


Figure 2. Fletcher and Peto graph of lung function decline

An interesting finding is that having a history of gastroesophageal reflux disease (GERD) or heartburn seems to correlate with the development of COPD exacerbations.[10] The pathogenesis of this is poorly understood, but may be related to a swallowing dysfunction. Although no studies have been conducted to evaluate whether treating these patients would help with COPD exacerbations, it is best to treat these patients with a trial of anti-reflux medicines.

Data from the COPD Gene study demonstrated that having chronic bronchitis doubles the frequency of COPD exacerbations.[11] Therefore, patients with a chronic bronchitis phenotype have a heightened risk and should be identified and followed-up closely. The COPD Gene study studied 10,000 people with COPD and conducted gene sequencing but it was not possible to identify a specific gene. In exacerbations one needs to consider other etiologies including pneumonia, congestive heart failure exacerbation, pulmonary emboli, as well as simply, non-compliance to prescribed medicines.[12]

The ECLIPSE study also reported that infections were responsible for approximately 50% of exacerbations. *Haemophilus influenza* along with *Streptococcus pneumoniae* and *Moraxella catarrhalis* were the most predominant. Patients with more severe disease were mainly affected by Pseudomonas infections. The role of *Staphylococcus aureus* and other Gram-negative bacteria is not well defined in exacerbations. It is also important to understand that some bacteria are colonizers and not actual pathogens. Previously, it was thought that COPD exacerbations were driven by a change in the concentration of bacteria; however, now we know that it is probably due to acquisition of new strains of bacteria.[13]

MANAGEMENT

The aim is to relieve symptoms, improve exercise tolerance and improve the overall health status. The main goals in the treatment of COPD include reducing the risks, preventing disease progression, preventing frequent exacerbations and reducing mortality. The pharmacological options in COPD are a growing field.[14]

Twenty years ago, the only treatment options were short-acting β-agonists, short-acting anti-muscarinics or a combination of both, in addition to theophylline and oral steroids. Nowadays, the list includes drugs such as long-acting bronchodilators (salmeterol, formoterol and once-daily indacaterol), inhaled corticosteroids (ICS) and phosphodiesterase inhibitors.

FEV_1 is no longer a comprehensive measurement of COPD disease. In a study by Westwood et al., there was a modest relationship between an increase in FEV_1 and improvements in the St George's Respiratory Questionnaire. This means that treatment effectiveness can be assessed at a study level;[15] however, from a practical point of view, this may be contradicted. For example, a patient may have an FEV_1 of 40%, yet their St George's Respiratory Questionnaire score may be almost normal, compared to another patient with the same FEV_1 who is disabled and terribly symptomatic.

Other tests, besides measuring the lung function, give a better idea of the disease activity and severity. The BODE index,[16] specific quality-of-life indices such as symptom rating scales, and also exercise testing can all give a better assessment

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

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

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** *The 92 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$- agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. *The 184 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. *For COPD:* One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** *Hypersensitivity* to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** ***Pregnancy:*** No adequate data available. ***Lactation:*** insufficient information available. ***Fertility:*** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom. **Marketing Authorisation Numbers:** EU/1/13/886/001-6. **DATE OF PREPARATION:** December 2013.

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

REPORTING ADVERSE EVENTS (AEs):

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

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

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

References: 1. Relvar Ellipta Summary of Product Characteristics. GlaxoSmithKline; 2016.

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

Relvar™ Ellipta™ was developed in collaboration with INNOVIVA

of the lung function. However, the limitations of these tests are that they are often difficult to perform in the clinic setting. The new GOLD guidelines recommend the Modified Medical Research Council Dyspnoea (MMRC) scale and the COPD Assessment Test (CAT) for use in the assessment of symptoms in COPD independently of FEV_1.

The UPLIFT study found that tiotropium, a bronchodilator, can actually cause a significant reduction of about 14% of exacerbations.[17] A study performed by Calverley et al. compared formoterol–budesonide versus formoterol alone in the reduction of symptoms, and found that the combination of a long-acting β-agonist (LABA) with ICS reduces COPD symptoms on a daily basis.[18] Further to this, the FLAME study[19] showed that the combination LABA with a long-acting muscarinic antagonist (LAMA) (indacaterol-glycopyrronium) showed consistent superiority to LABA-ICS (salmeterol-fluticasone) for outcomes of exacerbations, lung function and health status. Thus, it is important not to have strict categorization of these drug classes. There are also multiple new drugs that do not act on the symptoms but have a significant impact on reducing exacerbations, such as the recently introduced oral phosphodiesterase inhibitor, roflumilast.

HOW HAVE THE GUIDELINES CHANGED?

COPD is no longer measured just by using spirometry and FEV_1. The full picture should take in account the assessment of symptoms and exacerbations. Associated co-morbidities, which are potential factors, also need to be included in the patients' assessment. Subsequently, the best assessment of COPD is to combine FEV_1 and symptom severity (Fig. 3). In summary, group A has an FEV_1 that is still above 50%, exacerbations that are not frequent and they are generally not symptomatic.

Group B is the same, except that they have more symptoms. Group C has a lower FEV_1, along with frequent exacerbations or symptoms, whereas group D combines all parameters.

The difficulty arises in deciding on the pharmacological treatment for each group. Generally, group A patients receive short-acting bronchodilators, whereas group B must be given LAMA or a LABA, and groups C and D should take an ICS in combination.

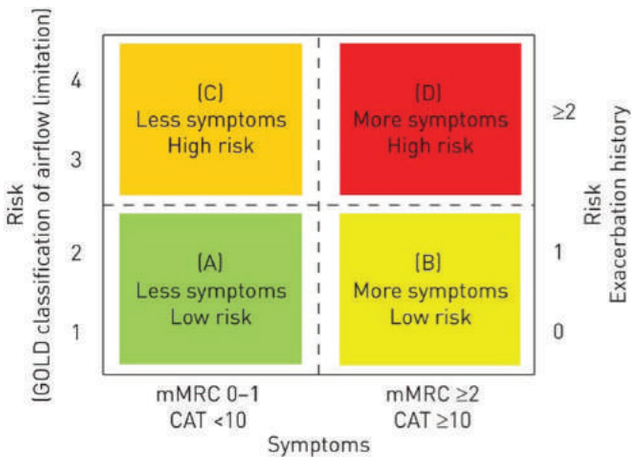


Figure 3. COPD Groups

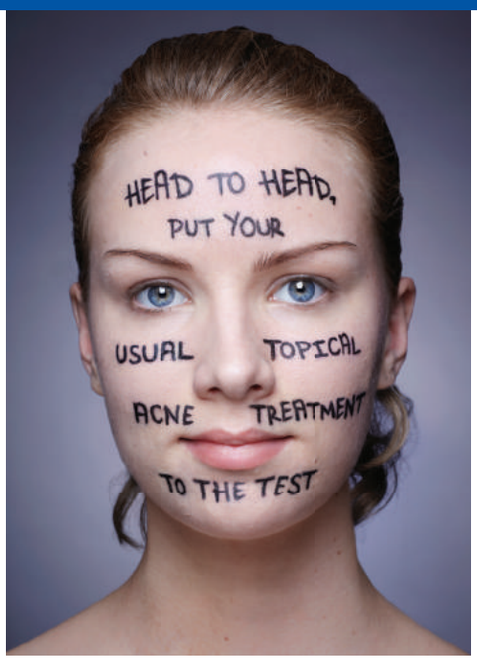
CONCLUSION

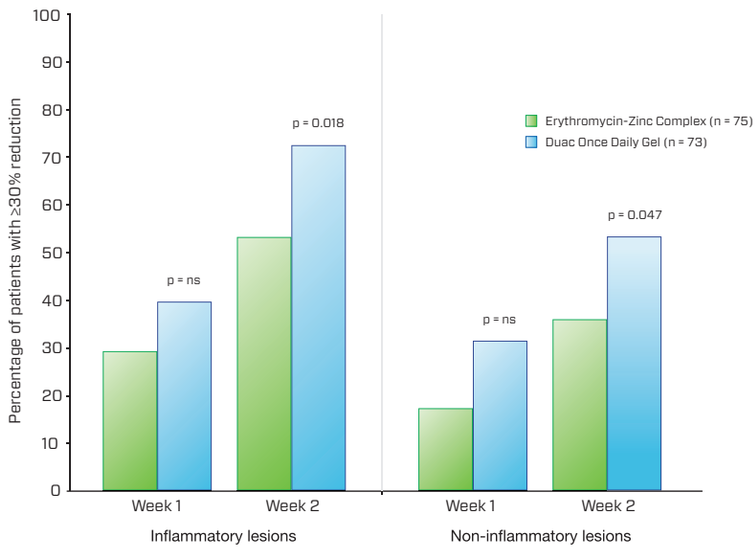
The disease progression of COPD should be explained to patients to help them overcome the denial of the causality of smoking. It is very important for patients to stay active; patients with symptomatic airflow obstruction should be offered a rehabilitation program as part of an optimal treatment plan.

It is difficult to treat dyspnoea or completely eliminate it, and this can require the use of double combinations of bronchodilators, i.e. LAMA plus LABA. If the patient does not respond, then a triple combination is recommended, with the addition of ICS. Some patients still do not improve, and one should consider adding a low dose of theophylline.[20,21] Sometimes, nebulized bronchodilators may help as a back-up management. The last resort remains the use of chronic oral corticosteroids; however, this is discouraged due to the side-effects.

When the problem relates to recurrent exacerbations, a combination of ICS plus LABA / phosphodiesterase inhibitor may be used, as well as the addition of prophylactic antibiotics.

HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX[1]





Graphs adapted from Langner A *et al.* JEADV 2007

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex[1]
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks[1]
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[4]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[3]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

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

TIPS[3]

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

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

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

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

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

Date of Preparation: January 2016

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 SPC, WHICH IS AVAILABLE FROM: GSK (MALTA) LIMITED (TEL: 21238131)

REPORTING ADVERSE EVENTS (AEs):

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

Stiefel a GSK company

For more information
www.hcp.gsk.com.mt/products/list/duac.html

Duac® once daily gel — *Clindamycin 1% and benzoyl peroxide 5%*

Job no.: MLT_GIB/CBP/0001/15a Date of preparation: October 2016

THE DISEASE PROGRESSION OF COPD SHOULD BE EXPLAINED TO PATIENTS TO HELP THEM OVERCOME THE DENIAL OF THE CAUSALITY OF SMOKING

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Serotonergic antidepressants insufficiently address the core depressive symptoms associated with "Decreased positive affect"[1]

Loss of pleasure, Loss of interest, Fatigue, Loss of energy

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

WELLBUTRIN XR – Abbreviated Prescribing Information: ***Please refer to full Summary of Product Characteristics (SmPC) before prescribing.*** **TRADE NAME:** Wellbutrin XR modified release tablets. **COMPOSITION:** Bupropion Hydrochloride 150mg and 300mg. **INDICATIONS:** Treatment of major depressive episodes. **POSOLOGY AND METHOD OF ADMINISTRATION:** Wellbutrin XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures. *Adults:* The recommended starting dose is 150mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300mg once daily. There should be an interval of at least 24 hours between successive doses. *Children and Adolescents:* Not indicated for use in children or adolescents aged less than 18 years. *Elderly Patients:* Same as adults but with greater sensitivity in some elderly individuals. *Hepatic and renal impairment:* 150mg once a day. *Discontinuing therapy:* A tapering off period may be considered. *Overdose:* Symptoms including drowsiness, loss of consciousness and/or ECG changes and rarely deaths even with large overdoses. **CONTRAINDICATIONS:** Hypersensitivity to buproprion or any of the excipients; co-administration with other medicinal products containing buproprion as the incidence of seizures is dose-dependent; current seizure disorder or history of seizures; known CNS tumor; withdrawal from alcohol or any medicinal product known to be associated with the risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **SPECIAL WARNINGS AND PRECAUTIONS:** Do not exceed the recommended dose of Wellbutrin XR especially in patients who have predisposing factors for seizures since the risk of seizures is dose-related. Not recommended/discontinued in patients who experience a seizure during treatment. Careful monitoring during the first weeks of treatment/dose changes/in patients with history of suicide-related events prior to treatment; discontinuation should be considered in cases of severe and sudden onset of suicidal ideation/behaviour. Wellbutrin XR should be discontinued promptly if patients experience hypersensitivity reactions during treatment; Use with caution in patients with hepatic and renal impairment. **INTERACTIONS:** Concomitant use with MAOI's is contraindicated; The dose of certain antidepressants, anti-psychotics, beta-blockers, SSRI's and Type 1C antiarrhythmics should be reduced when given concomitantly with Wellbutrin XR; Use with caution with cyclophosphamide and ticlopidine, carbamezapine, phenytoin, ritonavir, tamoxifen, valproate, levodopa or amantidine, alcohol and nicotine transdermal system. **ADVERSE EVENTS:** *Very Common:* Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting; *Common:* 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. *Not known:* suicidal ideation and suicidal behaviour. Refer to the SPC for a full list of adverse events. **PREGNANCY AND LACTATION:** Not recommended. **ABILITY TO DRIVE AND USE MACHINES:** Use with caution. **PRESENTATIONS:** Wellbutrin XR 150mg and 300mg x 30 tablets. **LEGAL CATEGORY:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, UK. **Marketing Authorisation Number:** MA 302/00101-2. **Date of preparation:** August 2016

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):

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

Put depression behind them.

References: 1. Nutt DJ, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, *et al.* The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol 2007; 21: 461–471.

Job No: MLT_GIB/BHC/0002/16a Prepared: October 2016

For more information
www.hcp.gsk.com.mt/products/list/wellbutrin.html

Wellbutrin® bupropion hydrochloride XR

The Noradrenaline & Dopamine Re-uptake Inhibitor.

WHAT ABOUT THE WEEDS?

Professor Everaldo Attard is perhaps one of the most eclectic persons Marika Azzopardi has met so far. His many hats are somewhat interlinked to certain facets of his life both professional and not, and yet all are somewhat distinct in character. So much so, this rich interview risked the requirement of a sequel. I meet him at the University of Malta, in his office from where he is not only an Associate Professor in Agricultural Chemistry & Pharmacognosy, but also co-ordinates the Division of Rural Sciences and Food Systems under the umbrella of the Institute of Earth Systems.

TS: CAN YOU TELL ME SOMETHING MORE ABOUT YOUR PROFESSION AND HOW IT DEVELOPED OVER THE YEARS?

I became a lecturer in 2001 after a long trajectory which kicked off upon my graduation as a pharmacist in 1994. My Master in Agriculture and Veterinary Pharmacy followed, which I completed in just one academic year. From research assistant I moved on to become assistant lecturer by which time I proceeded to acquire a Doctorate in Agriculture. I also held a temporary post as part-time consultant with the Department of Plant Health, and was eventually appointed Herbal Consultant for the assessment of herbal medicinal products. Presently I am also the Maltese delegate on the Committee on Herbal Medicinal Products (HMPC) within the European Medicines Agency and the Homeopathic Medicinal Products Working Group (HMPWG).

TS: I AM AWARE THAT YOU HAVE RESEARCHED A VERY UNIQUE LOCAL WEED - WHAT ABOUT IT?

Some years back my research was strongly linked to cancer research. Throughout my studies my focal point of research has been based on an indigenous plant with the common name of 'Faqqus il-Ħmir' (alias *Ecballium elaterium,* alias Squirting cucumber). Its anti-cancer properties came to the fore through my studies and elicited considerable scientific interest. Although it used to be a very ordinary 'weed' found growing prolifically around the Maltese Islands, it is nowadays less seen and only visible in abandoned areas. Although a common and nondescript plant in appearance, it intrigued me in that, although it belongs to the cucumber family and has pumpkins and melons on its family tree, it is of absolutely no culinary use. Indeed, its juice is especially bitter and toxic. However, it is a plant ingenuously armed to defend itself from all kinds of herbivores since once touched, its fruits will burst open and disperse a nasty tasting juice with seeds. This allows it to propagate itself in the process of self-protection. The only living creature which delights of its leaves is a ladybird with a specific identification name - the Gourd ladybird. Thus, back when I started my research of the 'Faqqus', its common presence and its self-defence technique interested me.

TS: ARE THERE ANY CURIOUS PAST AND PRESENT FACTS ASSOCIATED WITH THE 'FAQQUS'?

Yes, eventually I was to find out how, in olden days, the Maltese appreciated this weed for its laxative qualities and for the treatment of jaundice. At a certain point in time, it was actually exported to Germany for such purposes.

TS: WHAT IS THE STATE OF YOUR RESEARCH AT PRESENT?

My research eventually led me to conclude that while the anti-cancer properties of the 'Faqqus il-Ħmir' do exist to some extent, its terpenoids have more potentially healing qualities in the treatment of neurological conditions. This deviated the course of my research and I am in fact presently collaborating with a Canadian research team carrying out ongoing studies in this regard. One of my most recent research contributions has

been the publication of a paper entitled 'What are the Prospects of Treating Neurodegenerative Diseases with Natural Products?' (co-authored by Maria-Grazia Martinoli). This paper was published in July 2017 by ECronicon Open Access. Another recent paper, co-authored with Ritianne Spiteri, was published on the (Canadian) Journal of Agricultural Science and entitled 'Determination of Major and Minor Elements in Maltese Sheep, Goat and Cow Milk Using Microwave Plasma-Atomic Emission Spectrophotometry'. The latter topic touches upon my interest in local agricultural products and the beneficial potential therein. My research embraces local honey, cheeselets, olive oil, milk and certain fruits. A key concern is how we seem to be only purchasing foreign fruits most of the time, as well as a considerable amount of vegetables, whilst somewhat putting local agriculture to the side. This is wrong and should be seen to.

TS: SO WHERE DOES ALL THIS LEAVE YOUR PHARMACY WORK?

In reality I was a fully employed pharmacist for only six months upon graduation. I did locums for some time but nowadays, I keep abreast with pharmaceutical progress through my work with the Medicines Authority which places me on the other edge of the pharmaceutical spectrum. Such work relates to the assessment of herbal medicines, especially in the classification of borderline products. My presence at the HMPC in London and the HMPWG ensures that I keep working at making the two ends meet - the one part where nobody believes in the efficacy of natural products, herbal medicines and food supplements and the other part where nobody trusts the modern pharmaceutical product. Natural products are excellent for long-term use as long as dosage and follow-up are adhered to. But nothing beats modern medicinals for the efficacy in emergency intervention. Internet sources can be misguiding and at times completely incorrect and this misleads the general public in thinking that natural remedies are good, always, all of the time.

TS: CAN YOU SPECIFY MORE ON THIS ASPECT OF NATURAL REMEDIES?

A plant growing in the wild may contain toxins and heavy metals absorbed from its environment and from the soil. Picking it up and using it, may be dangerous. Moreover one requires a good diagnosis and the right dosage for it to be effective.

TS: EARLIER ON YOU REFERRED TO HOMEOPATHY. WHAT IS THE STATE OF AFFAIRS IN THAT AREA?

One clarification should be made here - one still needs a medical degree in order to diagnose a patient before prescribing homeopathic remedies. This field is still ambiguous in medical terms and the scrutiny is on the dilution factor applied to tinctures. Homeopathy uses the same principles as vaccines; however, dosages are minuscule. Where dilution goes below the presence of molecules in the actual product, there is a strong element of doubt. There are however, entire hospitals for humans and for animals, which practise this type of therapy with success.

TS: YOUR WORK AND ACADEMIA DEFINITELY KEEP YOU BUSY. BUT IS YOUR LIFE ONLY AND UNIQUELY ABOUT SCIENCE?

Thankfully not. I find time to unwind by singing as a member of the Amadeus Chamber Choir directed by Maestro Brian Cefai. It all started when my son began singing in the choir. My wife joined, then my daughter, and somehow I got roped in as well. In actual fact I find it to be a great de-stressor, quite different from correcting papers and carrying research. And it is a good way to socialise. Indeed, I have met many singers who come from all walks of life … even some acquaintances I never knew were actually in a choir.

I READ THE SYNAPSE BECAUSE...

It provides the professional reader with on-going knowledge in the field of medicine, and gets you to know people through the various interesting articles presented within.

Actifed*

Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders [1-7]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [3,6]

Actifed* SYRUP AND TABLETS

- clears blocked and runny noses [2,5]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [4,7]

DOSAGE		
LIQUIDS	children aged 2 to 5 years [2-4]	2.5ml every 4-6hrs as required
	children aged 6 to 11 years [2-4]	5ml every 4-6hrs as required
	adults (including the elderly) and children aged 12 years and over [5-7]	10ml every 4-6hrs as required
TABLETS	adults (including the elderly) and children aged 12 years and over [1]	1 tablet every 4-6hrs as required

OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: *Please refer to full Summary of Product Characteristics (SPC) before prescribing.* **TRADE NAME:** ACTIFED**. ACTIVE INGREDIENT:** *Actifed DM Cough Linctus:* Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Syrup:* Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; *Actifed Expectorant:* Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg; *Actifed Tablets:* Each tablet contains Pseudoephedrine Hydrochloride 60mg; Triprolidine Hydrochloride 2.5mg**. PHARMACEUTICAL FORM:** Oral Solution and Tablets**. INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of: Actifed DM Linctus: a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; Actifed Expectorant: a nasal decongestant, an anti-histamine and an expectorant; Actifed Tablets: a nasal decongestant, and an anti-histamine**. DOSAGE:** *please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant* are authorised for use without the need of a medical prescription in Adults and Children over 12 years**.** In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor**. CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of MAOI's in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure**. PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment**. INTERACTIONS:** Sympathomimetics; MAOI's**. ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement**. PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child**. PRESENTATION:** *DM Cough Linctus, Expectorant, Syrup:* Amber glass bottle x 100ml; Tablets: Pack x 24 tablets. Marketing Authorisation Holder: Glaxo Wellcome UK Limited, **Marketing Authorisation Number:** MA 167/00101**-7 Legal category:** POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years**. For further information and full prescribing information contact GlaxoSmithKline (Malta)** Ltd: Tel**.** 21238131**. Date of preparation:** January 2015

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References: 1. Actifed Tablets SPC (Apr 2014); 2. Actifed Syrup SPC (Mar 2015); 3. Actifed DM Cough Linctus SPC (Jan 2015); 4. Actifed Expectorant SPC (Jan 2015); 5. Actifed Syrup SPC OTC (Mar 2015); 6. Actifed DM Cough Linctus SPC OTC (Jan 2015); 7. Actifed Expectorant SPC OTC (Jan 2015)

Job No: MLT_GIB/PDH/0005/16 Date of preparation: February 2016

DETECTING BREAST CANCER: 2D VS 3D IMAGING

PIERRE VASSALLO

BACKGROUND OF THE BREAST CANCER AWARENESS MONTH

The month of October has become synonymous with an increased awareness of breast cancer. The amount of information presented on the media about breast cancer during the month of October is frequently overwhelming and often confusing. We should not be *more* aware of breast cancer during October, simply because the incidence of breast cancer is the same all year around. However, October serves as a yearly wake-up call to the importance of being proactive in the detection and treatment of breast cancer. It has also become a calendar event for organising fund-raising activities for breast cancer treatment and research.

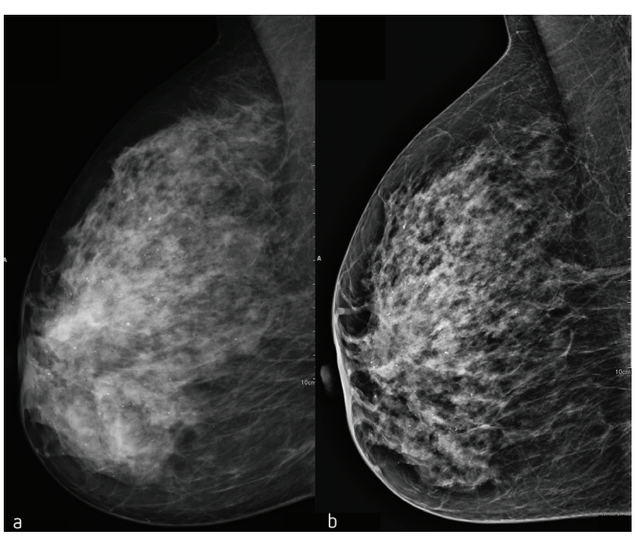

Figure 1. CR Mammogram (a) versus FFD Mammogram (b). Note the superior image clarity in (b).

The concept of having a Breast Cancer Awareness Month was born in 1985 through cooperation between the American Cancer Society and Astra Zeneca, a pharmaceutical company that was developing breast cancer medicines. Initially, the aim was to promote screening with mammography for the early detection of breast cancer and to institute treatment early. In 1993, the Breast Cancer Research Foundation was created in the US to source funds for research in breast cancer; the foundation and similar societies throughout the world use the month of October to promote awareness through education and to organise events to raise funds for breast cancer research.

The month of October sees an abundance of educational and promotional information appearing in all the media from governmental and private organisations that is aimed at enhancing the public awareness of the importance of detecting breast cancer early and how this is done. Organisations use this month to promote the use of well-established technologies for breast cancer detection. Unfortunately, this month is also used by some companies to showcase newly acquired "innovative" technologies that have no scientifically proven clinical advantage.

The article below outlines the well-established and scientifically proven technologies, as well as the newer ones, and guides the reader on which test should be performed based on patient age and clinical background.

WHY IS BREAST IMAGING IMPORTANT?

The answer is short and simple: it reduces the mortality of breast cancer.

Breast cancer is one of the leading causes of death in women worldwide.[1] In 2002, Duffy *et al* reported that breast cancer

screening reduced the mortality from breast cancer by 45%.[2] This statistic was derived at a time when only mammography was used and the quality of mammography was far inferior to the image quality obtained by mammography today. With modern mammographic methods, we should improve on the above quoted findings. However, with the development of multiple new techniques for breast cancer screening, it is becoming increasingly important to select the right technique based on the patients' needs. Having multiple technologies at hand is often leading to a degree of confusion that may delay diagnosis and treatment.

TECHNOLOGIES AVAILABLE FOR BREAST CANCER DETECTION

MAMMOGRAPHY

Mammography is overall still the best tool for breast cancer screening, however, it is important to know its limitations and when to use ancillary imaging techniques to improve diagnostic accuracy.

Mammographic images have seen big improvements in quality resulting from technological development over the past two decades. The shift from conventional film/screen mammography to digital mammography resulted in improvement in image quality and reduction of radiation exposure. Digital mammography underwent further development from Computed Radiography (CR) Mammography to Full Field Digital (FFD) Mammography. The introduction of FFD mammograms brought about the biggest overall improvement in image quality and in diagnostic accuracy.

When referring to mammography today, we should no longer consider performing film/screen mammograms or CR mammograms as they are diagnostically inferior to FFD mammograms (Fig 1). Only FFD mammograms should be performed today.

FFD mammograms are low dose X-ray images of the breast that depict internal structure based on tissue density. There are two main types of normal tissue in the breast, breast glands and ducts which are dense, and fat which is low density. The overall density of the breast reflects the proportion of glands/ducts to fat. Very glandular breasts are dense, while very fatty breasts are non-dense.

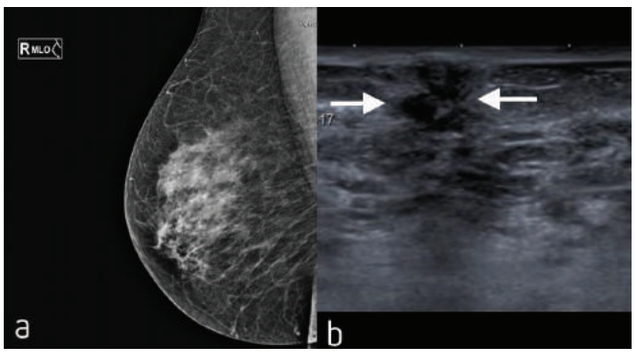

Figure 2. FFD Mammogram showing a moderately dense breast that obscures a clinically noted medial breast nodule (a) and ancillary imaging with ultrasound (b) confirming the presence of a small cancer (arrows).

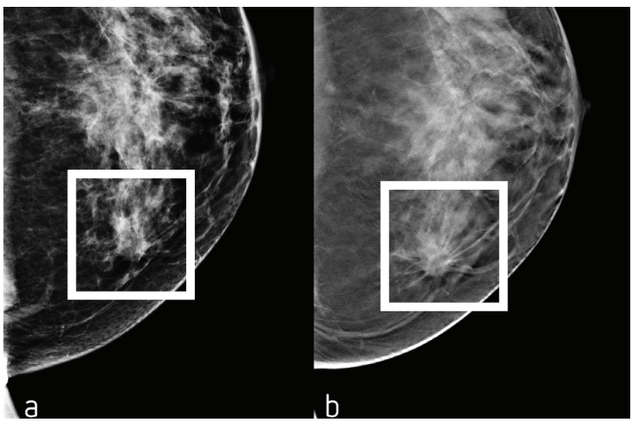

Figure 3. FFD (2D) Mammogram (a) versus Tomosynthesis (b): Tomosynthesis may be used as an ancillary test to evaluate abnormalities detected on FFD mammograms; note cancer (in box) seen on both images.

Cancers are dense on mammograms and are hence better seen on a fatty background than on a glandular background. In the case of very dense breasts, which may account for 20-40% of the screening population, cancers may be difficult to detect and may require additional imaging methods to ensure an accurate diagnosis.

The most cost-effective and efficient ancillary imaging method for dense breasts, when combined FFD mammograms, is breast ultrasound (Fig 2). This is quick and poses no additional radiation exposure to the patient. It can also be used to guide immediate biopsy to expedite further management.

Recent years have seen the development of breast Tomosynthesis ("3D mammograms"), which is a further development of digital mammographic technology; this system obtains image slices through the breast to reduce overlap of glandular tissue (Fig 3). Tomosynthesis is beneficial when combined with FFD mammography for dense breasts, but since it is done following FFD mammography, this results in doubling of the radiation exposure dose to the patient. Besides, proceeding to a breast ultrasound instead of Tomosynthesis often delivers the same results, while reducing the radiation exposure and cost. Ultrasound also has the added advantage of allowing efficient and immediate biopsy that expedites management.

To date, the use of Tomosynthesis alone has not be clinically accepted as a primary screening method for breast cancer.

BREAST ULTRASOUND

Breast ultrasound is a valuable adjunct to FFD mammography when screening for breast cancer.[3] Combining the two tests increases diagnostic accuracy particularly in dense breasts.

Breast ultrasound alone may be used for screening younger women (<40 years of age), particularly for those who have very dense breasts and for those who have breast implants.

Beast ultrasound is a test that requires *direct hands-on intervention by a breast radiologist*. The radiologist should be experienced in performing breast ultrasound, should be aware of any relevant clinical symptoms or findings before performing the scan,

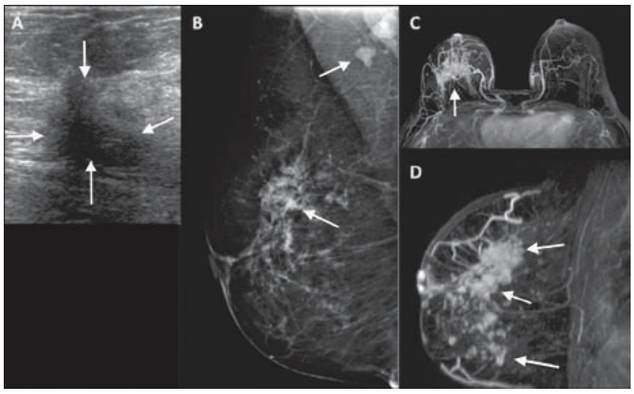

Figure 4. Breast Ultrasound (A), FFD Mammogram (B) and Breast MRI (C and D): The images show a less common type of breast cancer, an invasive lobular cancer; this type of cancer is poorly seen on FFD mammograms (B) but is detected by breast ultrasound (A). However, its full extent can only be seen on Breast MRI (C and D); it involves the whole right breast (arrows). Breast MRI is the only test that accurately assesses the extent of lobular breast cancer.

should ensure full coverage of all breast tissue and axillary regions and should maintain open communication with the patient during the scan as she may provide information that could be relevant to the procedure. The radiologist should be aware of all mammographic findings and should have correlated those findings with previous exams prior to performing an adjunct breast ultrasound scan.

Any attempts at saving radiologist time by employing ultrasound technologists or automated breast ultrasound scanners (ABUS or 3D scanners) results in loss of this open clinical encounter, with the ensuing risk of loosing valuable information from the diagnostic process. The radiologist should have direct access to the patient, must review previous mammograms and must perform the ultrasound scan to ensure that all sources of data are integrated to deliver the most accurate diagnosis.

ABUS scanners have been in the market for the past 10 years; they have not yet been shown to be reliable enough to replace normal breast ultrasound for breast cancer screening. There are numerous issues that limit the value of ABUS as a diagnostic test: (1) There are risks that the scan will not cover the whole breast, particularly the axillary regions; (2) in saving radiologist's time, it reduces communication between the patient and the radiologist, which may result in clinical findings such as skin puckering, nipple discharge or a nodule being missed; (3) artefacts that occur during a normal ultrasound scan can be minimised by an experienced radiologist through changes in scanning angle and scanner settings; this is not possible with ABUS. If a scan is performed by technologist or a machine (in case of ABUS), mammographic and clinical data are not integrated to improve the accuracy of the ultrasound scan.

BREAST MRI

Breast MRI is the most sensitive test for detecting breast abnormalities. Certain types of breast cancer, such as early ductal carcinoma-in-situ and lobular breast cancer can only be reliably detected by MRI. Breast MRI, however, requires an expensive scanner, has prolonged examination times in an uncomfortable position and requires the use of an injection of contrast material. Breast MRI also detects many benign nodules as well as malignant ones, which may occasionally result in unnecessary further investigation. Still, breast MRI remains the best test to use for dense breasts (Fig 4). Breast MRI is still considered to be too costly and time-consuming to be used as a routine breast cancer screening tool; it is an excellent method for diagnostic workup of equivocal findings and for imaging certain types of breast cancer.

SELECTING PATIENTS BASED ON AGE

When deciding on the best test for breast cancer screening one starts by checking the patient's age.

For patients aged 40 years or older, breast cancer screening should start with a FFD mammogram. This should be reviewed immediately by a breast radiologist, who then proceeds to a direct hands-on breast ultrasound if any mammographically equivocal or suspicious findings are detected. Interaction between the radiologist and the patient is important at this stage as it may contribute significant information to the diagnostic process and will help reduce the patient's stress. Proceeding to Tomosynthesis before performing an ultrasound may lead to unnecessary radiation exposure. Proceeding to a breast MRI or an ultrasound-guided biopsy may also be more efficient than employing Tomosynthesis.

For patients under the age of 40 years, a breast ultrasound should be the first examination with direct, hands-on intervention by a breast radiologist to ensure that both clinical and ultrasound findings are integrated into the final report and treatment recommendations. Further investigations, if doubts arise on the ultrasound, may include ultrasound-guided biopsy or breast MRI. Mammograms are occasionally performed in this age group, but they often contribute less information since many of these patients have dense breast.

CONCLUSION

In summary, FFD mammograms (2D mammograms) are fundamental to all breast cancer screening programs, particularly since these programs are recommended for women aged 40 years and older. They are the best tool we have for detecting breast cancer. Direct hands-on breast ultrasound (2D ultrasound) performed by an experienced breast specialist contributes important data when combined with FFD mammograms and expedites management while avoiding additional radiation exposure.

Tomosynthesis (3D mammograms) should only be used as an ancillary test if findings on 2D mammograms and 2D breast ultrasound are still unclear. Automated Breast Ultrasound (ABUS or 3D ultrasound) does not replace direct hands-on 2D breast ultrasound as it will lead to loss of valuable diagnostic information that may delay treatment.

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