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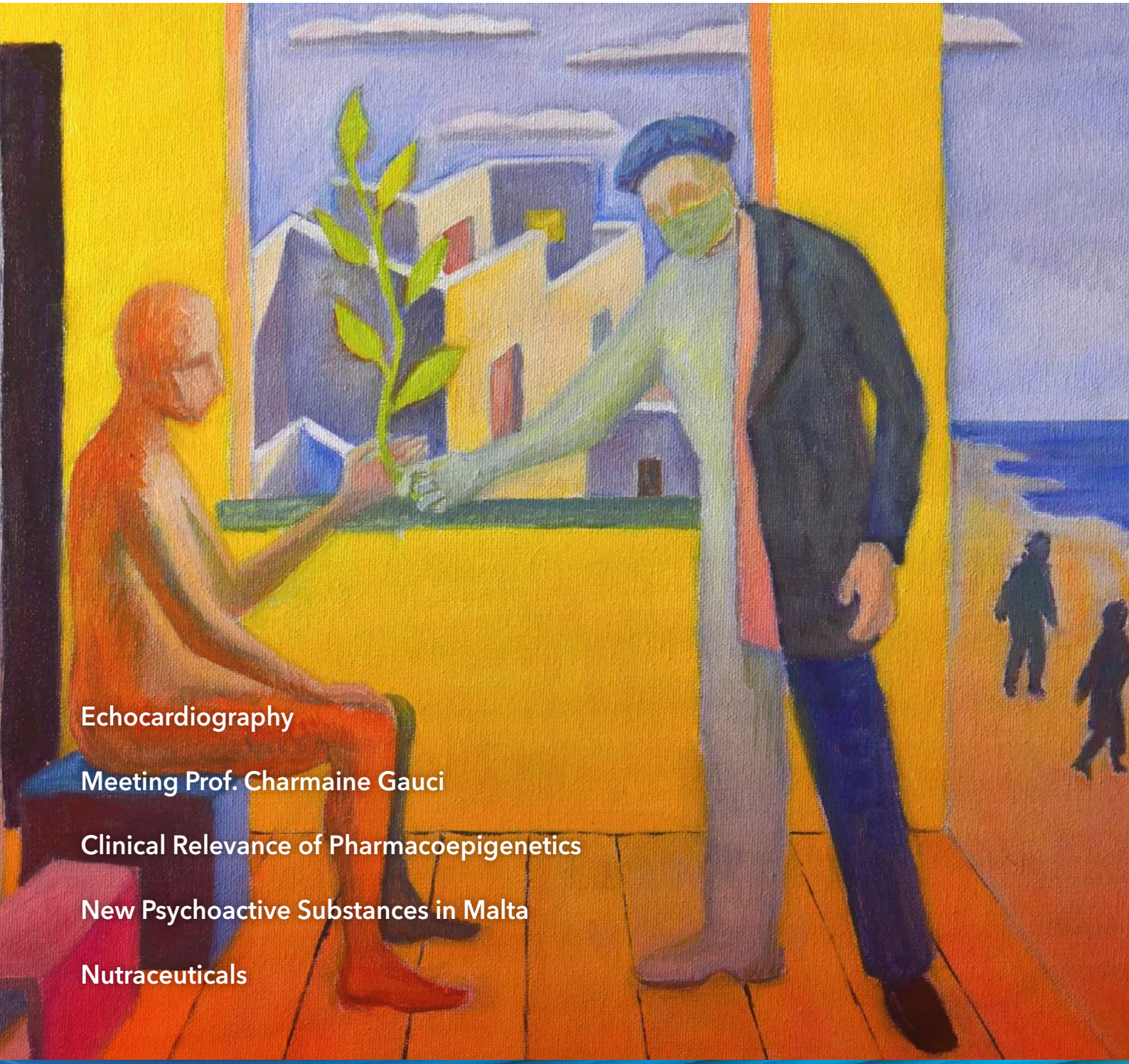
thesynapse

THE MEDICAL PROFESSIONALS' NETWORK



Echocardiography

Meeting Prof. Charmaine Gauci

Clinical Relevance of Pharmacoepigenetics

New Psychoactive Substances in Malta

Nutraceuticals

Helping people with MDD* rediscover the love for life

Bupropion has a lower incidence of sexual side-effects compared with the other SSRIs in MDD* patients^, 1, 2

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.[3]
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.[3]

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-190001
Prepared: April 2019

References:
* MDD: Major Depressive Disorder; SSRI: selective serotonin reuptake inhibitor
^ SSRIs: sertraline, citalopram, escitalopram, paroxetine and fluoxetine
1. Clayton AH et al. Prevalence of sexual dysfunction among newer antidepressants, J Clin Psych,2002;63:357-366
2. Clayton AH et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry. 2006;67(5):736-46
3. Wellbutrin XR SPC (Nov 2018)

Wellbutrin® bupropion hydrochloride XR

The only Noradrenaline & Dopamine Re-uptake Inhibitor.

Authors

Dr Andrew Cassar Maempel MD, FRCP(Edin), FACC, FSCAI, FESC is a consultant cardiologist who completed specialist training in general and interventional cardiology at the Mayo Clinic in the US. He provides preventative, diagnostic (echocardiogram, stress testing, Holter monitor and cardiac CT angiography) and therapeutic cardiology services (cardiac catheterization, stenting and pacemaker placement). He is academically active in both teaching and research and has published multiple papers in top cardiology journals.

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Issue Guide

Cover:
Giving Hope, Oil on canvas 50 x 40cm.
In this epidemic, the healthcare professional is putting all aside to deliver hope to the patient, where hope is represented by a branch with leaves.

John Michael Caruana studied art and printmaking at the Malta School of Art in Valletta. He uses various media including oils, acrylic, watercolour and charcoal. His preferred techniques in printmaking are aquatint and aquaforte. John graduated in pharmacy in 1992.

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EDITORIAL

Of Covid-19 and Inflection Points

SARS-CoV-2 is the latest addition to the family of coronaviruses - enveloped positive-sense RNA viruses – first identified in the 1960's. In a few weeks it has managed to shrink the GDP of the entire world. It exposed the economic fragility of some countries, yet showcased the resilience of others (including Malta). Key to this poise is the ability to mitigate the challenges posed by the pandemic on healthcare systems and social fabric.

SARS-CoV-2 has brought the entire world to its knees for various reasons. It is highly contagious which can spread even through pre-symptomatic and asymptomatic transmission. Apart from the classic symptoms, case reports have described covid-19 patients initially presenting with symptoms ranging from thrombotic events, cardiac inflammation to renal insufficiency. In children, a Kawasaki-related disease has also been reported. This can make early diagnosis challenging, especially in the community setting. Other factors including globalisation and an ageing population [with ensuing health complications] certainly precipitated the onset of the pandemic.

We have also witnessed the lack of healthcare preparedness in some countries, general complacency in others, and at times conflicting messages delivered by policy leaders still in others. Of note is the meagre statistics and information divulged by specific countries which have been initially affected by the disease which could have delayed action and ensuing research. In keeping with this, numerous countries have called for an investigation into the origins of the pandemic.

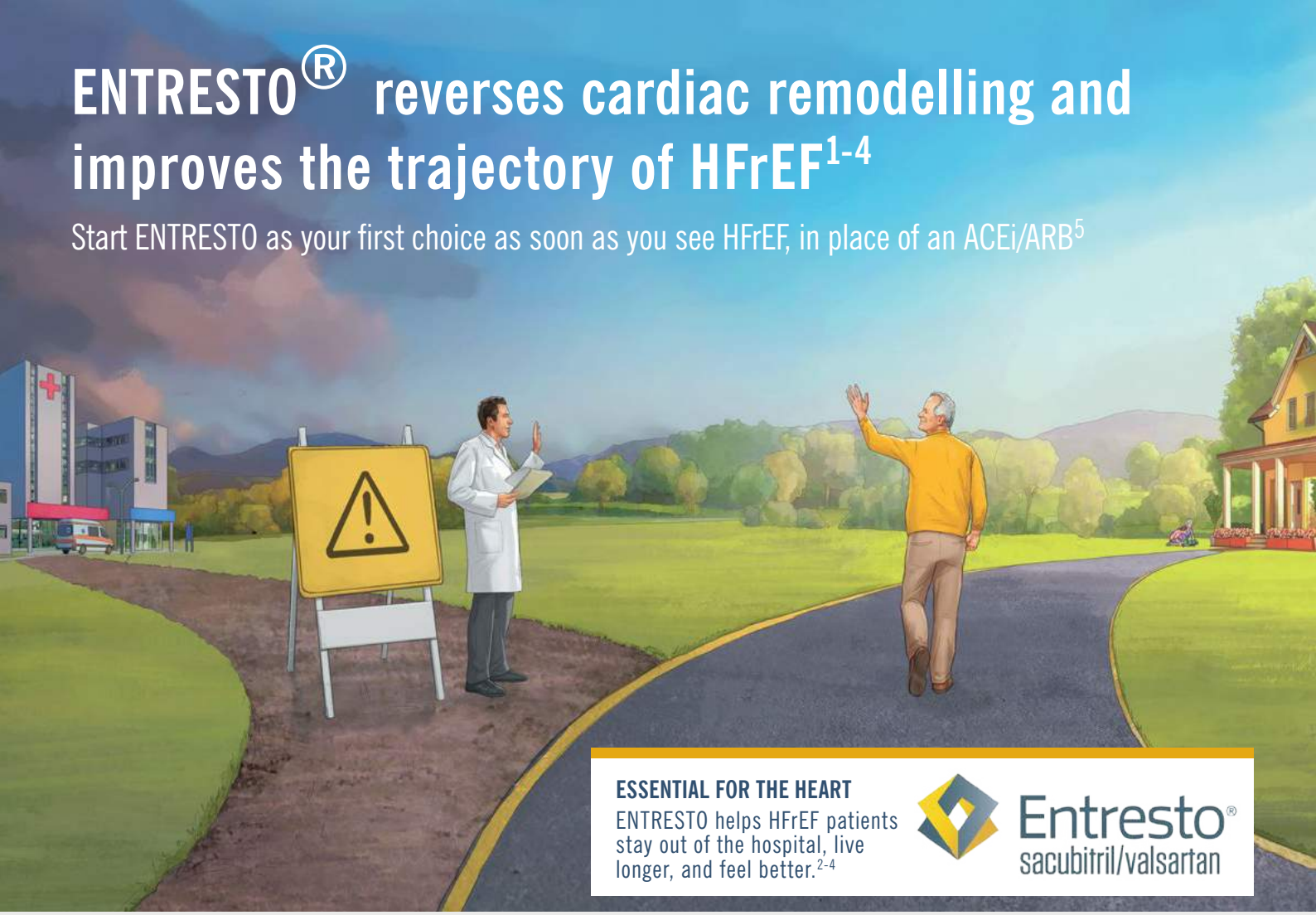
This leads me on to the next point … the paradigm shift in the machinery of science which we are experiencing. The number of publications relating to Covid-19 has been fast and gargantuan [close to 10,000 papers]; this is largely attributed to preprints which are being made readily available and free-of-charge prior to peer review. Although the practice of preprints in the medical field has always been a bone of contention, recent studies have shown that the difference in scientific value between preprints and the final version, following peer review, can be minimal. An advantage of preprints is that experts from *different fields* can criticize and 'dissect' the research; to a certain degree, this leads to self-regulation. Most importantly, preprints accelerate collaboration between researchers, which in turn, churns 'real-time' data and this, in turn, yield important information which is then used by policy makers from all over the world to make decisions. In essence, this pandemic effectively seems to be changing the manner in which scientists conduct their work and collaborate. It is the opinion of several leading academics that such practice is here to stay.

At this stage, the kernel of the matter is when a vaccine [or vaccines] will be licensed. Currently, to date, there are over 80 vaccines under development. In keeping with this, last May the EU raised $8bn in pledges from worldwide donors to finance the collaborative development and universal deployment of diagnostics, treatments and vaccines against covid-19 [the US and China did not pledge any money]. Malta committed €400k. Interestingly, in April, Serum Institute of India, the world's biggest vaccine maker by volume, announced that it will start manufacturing a vaccine currently being developed by Oxford University when clinical trials reach Phase III, if effectiveness is proved.

In another editorial we will discuss immunity passports and excess mortality measurements. The latter are used to identify reporting lacunae, which may stem from varying death-certification procedures in various countries, that effectively undermine any correct analysis of real-time covid-19 deaths, especially in nursing homes. In the meantime,
stay healthy and safe!

ENTRESTO® reverses cardiac remodelling and improves the trajectory of HFrEF[1-4]

Start ENTRESTO as your first choice as soon as you see HFrEF, in place of an ACEi/ARB[5]



ESSENTIAL FOR THE HEART

ENTRESTO helps HFrEF patients stay out of the hospital, live longer, and feel better.[2-4]

Entresto®
sacubitril/valsartan

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; HFrEF=heart failure with reduced ejection fraction.

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 coadministered 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, 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

References: 1. Januzzi JL Jr, Prescott MF, Butler J, et al; for the PROVE-HF Investigators. Association of change in N-terminal pro–b-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA. 2019;322(11):1085-1095. 2. Claggett B, Packer M, McMurray JJV, et al; for the PARADIGM-HF Investigators. Estimating the long-term treatment benefits of sacubitril–valsartan. N Engl J Med. 2015;373(23):2289-2290. 3. Lewis EF, Claggett BL, McMurray JJV, et al. Health-related quality of life outcomes in PARADIGM-HF.Circ Heart Fail. 2017;10(8):e003430. 4. ENTRESTO Summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu. Accessed 2018. 5. Seferovic PM, Ponikowski P, Anker SD, etal. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21(10):1169-1186.

NOVARTIS

ENT AD1 04/20 MT

my MedRep

24/7 LINK BETWEEN MEDICAL PROFESSIONALS AND MEDICAL REPRESENTATIVES

thesynapse.net/mymedrep

The Covid-19 pandemic has presented several challenges for both medical professionals and medical representatives. This has kickstarted a collaboration between TheSynapse and the Association of Medical Representatives to launch **MyMedRep**, available at **thesynapse.net/mymedrep**.

MyMedRep is an innovative on-demand 24/7 communication channel between medical professionals and medical representatives aimed at facilitating the relay of fine-grained information in an expedited manner.

At the basic level **MyMedRep** contains information on medical representatives practising in Malta i.e. photo, contact details, company name, as well as the marketing authorisation holder/s represented by the medical representative. These details are updated by the Association of Medical Representatives and the pharmaceutical industry. A more advanced plan contains a multi-channel communication system including offline contact forms, a platform for online video-based meetings, as well as information repository facilities.

WHY SHOULD MEDICAL PROFESSIONALS USE MYMEDREP?

1. It is free of charge and makes you save time … the frequency of medical representatives' visits is minimised, leaving you more time to dedicate to your patients.
2. **MyMedRep** is very easy to use. You only need to access the web portal on any device - even mobile phones - and identify a medical representative. One can then book a video meeting by simply clicking on the medical representative (convenient pre-defined time slots).
3. This on-demand tool also allows you to interact with medical representatives whenever the need arises through a unique online portal which is available 24/7. You can use the service to make enquiries relating to sample requests, product literature information, educational interventions and support, etc.
4. **MyMedRep** is also an information repository. You may access scientific literature, product information or explainer videos uploaded by medical representatives - on a desktop or other mobile device - at your convenience whenever you need them.

WHY SHOULD MEDICAL REPRESENTATIVES USE MYMEDREP?

1. It simply makes you save time since clinic waiting time is drastically reduced.
2. It effectively overcomes any challenges related to social distancing, which will remain with us for the foreseeable future.
3. Studies have shown that virtual meetings between medical representatives and doctors generally have a longer duration of visit than face-to-face meetings, stemming from the fact that doctors schedule meetings at their convenience and are in control of the meetings' duration.
4. Clinic visits can be reinforced through e-detailing through **MyMedRep** since it allows you to interact with doctors whenever the need arises through a unique online portal which is available 24/7. In keeping with this, this on-demand platform will aid intelligence gathering and will strengthen the working relationship between you and physicians.
5. **MyMedRep** is also an information repository. You may upload scientific literature and information on the web portal at your convenience which can be accessed by medical professionals when they need it. Furthermore, you may also post explainer videos for doctors relating to e.g. Risk Management Plans of specific products, Dear Doctor Letters, etc.
6. **MyMedRep** allows you to hold virtual meetings with a number of doctors simultaneously. This means that you can hold an evening presentation on a specific product, with the guest speaker hailing from Japan or the US and local medical professionals – back at home after a long day's work - in Malta & Gozo.

ABOUT THE ASSOCIATION OF MEDICAL REPRESENTATIVES

The Association of Medical Representatives (AMR) is formed by members who are full-time or part-time medical representatives by profession in Malta. The AMR was set up in the late 1980's and its main objective is to provide a central organization for medical representatives. A five-member committee is elected at the AGM. Every member upon subscription is given a membership card which can in turn be used to enter government health institutions. Subject to the provisions of the Memorandum, every member of the Association abides by the Association's rules and Code of Ethics.

ABOUT THESYNAPSE NETWORK

Since 1996, TheSynapse Network has been an established, premiere provider of news as well as Online Continuing Medical Education for Medical Professionals. We pride ourselves on our experience, multichannel approach to reaching our members, our versatility and above all, our members' trust.

DR ANDREW CASSAR MAEMPEL

Echocardiography

Key words: Transthoracic, Transoesophageal, Stress, Echocardiography, Doppler

ABSTRACT

Despite advances in novel cardiac imaging techniques, echocardiography remains the primary non-invasive imaging modality to assess cardiac structure and function. It is readily available, portable and yet gives comprehensive quantitative and qualitative evaluation of cardiac anatomy and function. It is also highly adaptable to be implemented in multiple modalities such as transthoracically, transoesophageally or in conjunction with stress (exercise or pharmacological). The following is a succinct review of echocardiography for the interested physician.

INTRODUCTION

Echocardiography is the imaging of cardiac structures using high frequency (>1Mhz) acoustic waves. Acoustic waves are produced by piezoelectric crystals in a transducer which reflect off cardiac structures and return to the transducer were signals are transformed to images. The most important technical aspect of echocardiography is its high sampling rate (>1kHz) and thus excellent temporal resolution, allowing accurate imaging of the cardiac structures throughout the cardiac cycle. This imaging technique can be performed transthoracically or tranoesophageally.

A. TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic Echocardiography (TTE) has become a key component of routine evaluation of patients with suspected or known cardiovascular disease. Its availability,

Table 1 - Indications for Transthoracic Echocardiography

1. Symptoms
Chest pain
Shortness of breath
Palpitations
Presyncope/Syncope
Lower extremity swelling
2. Heart murmur
3. Abnormal ECG
4. Hypertension
5. Screening for elite athletes
6. Screening for inherited diseases

portability, ease of use and lack of radiation make it a safe and immediately available imaging tool to help the caring physician with diagnosis and management of the patient. Indications for TTE are listed in Table 1. It gives essential information on both cardiac structure (chamber size and wall thickness, valve pathology, pericardial thickening or effusion, aortic size and pathology, cardiac masses or thrombus) and function (left and right ventricular systolic and diastolic function, left ventricular outflow obstruction, valvular stenosis and regurgitation, cardiac tamponade, constrictive or restrictive physiology and pulmonary pressures). Multiple images are taken from 4 main echocardiographic windows – left parasternal (Figures 1A-C), apical (Figure 1D), subcostal (Figure 1E) and suprasternal (Figure 1F) windows. Different echocardiographic modalities are available to obtain as much information as possible. M-mode echocardiography (Figure 1A) depicts a single line of ultrasonic data over time. It has high sampling rate and superb temporal resolution and is useful to measure chamber dimensions and timing events in the cardiac cycle. M-mode has been nearly totally replaced by two-dimensional (2-D) imaging (Figures 1B-F).

2-D imaging is the result of interpolating data between multiple scan lines to give a sector image of the heart and reiterative acquisition over the cardiac cycle results in a live movie of the heart. Harmonic tissue imaging is further used to enhance image resolution by eliminating artifact and improving signal-to-noise ratio. 2-D imaging allows for global functional assessment such as for left ventricular ejection fraction estimation and for assessment of wall motions to exclude regional wall motion abnormalities.

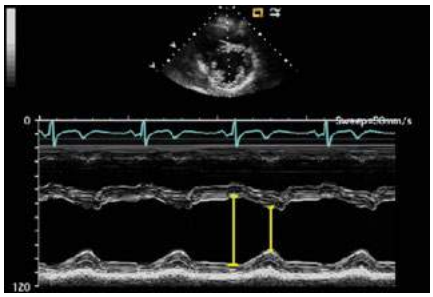


Figure 1A. M-mode measuring left ventricular dimensions in diastole and systole which can be used to calculate left ventricular ejection fraction

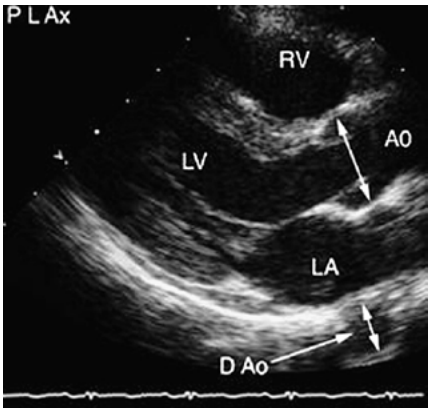


Figure 1B. 2-D echocardiography in the parasternal long axis view. LV= left ventricle, RV= right ventricle, LA= left atrium, Ao= aorta, D Ao = descending aorta

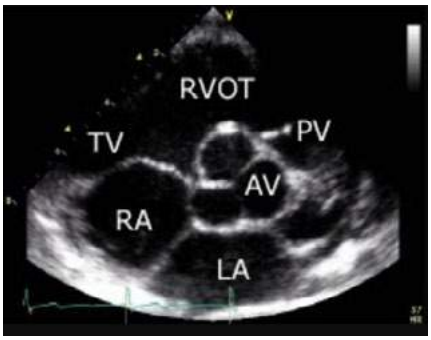


Figure 1C. 2-D echocardiography in the parasternal short axis view at the base of the heart. AV = aortic valve, LA = left atrium, RA = right atrium, TV = tricuspid valve, RVOT = right ventricular outflow tract, PV = pulmonary valve

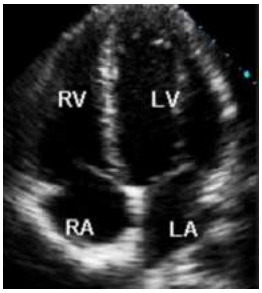


Figure 1D. 2-D echocardiography in the apical 4 chamber view. LV = left ventricle, RV = right ventricle, LA = left atrium and RA = right atrium

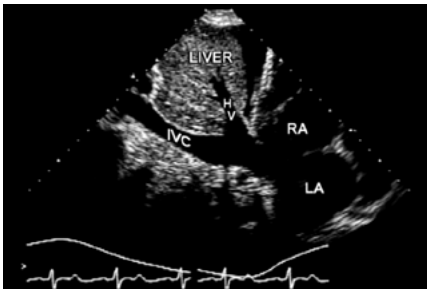


Figure 1E. 2-D echocardiogram in the subcostal view. IVC = inferior vena cava, HV = hepatic vein, RA = right atrium, LA = left atrium

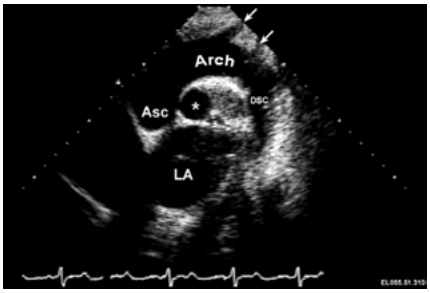


Figure 1F. 2-D echocardiography in the suprasternal long axis view. Asc = Ascending aorta, Arch = arch of aorta, Desc = descending aorta, LA = left atrium, * = left pulmonary artery

Global left ventricular systolic function is classified as hyperdynamic (=>75%), normal (55-74%), mildly decreased (46-54%), moderately decreased (36-45%) and severely decreased (<=35%). The left ventricular myocardium is divided into 17 standardized segments. Regional wall segments are classified as normal, hypokinetic, akinetic, dyskinetic or aneurysmal, and abnormalities are suggestive of underlying coronary artery disease. A hyperechogenic thinned area suggests the presence of scarring. 2-D imaging suffices for most routine echocardiograms, but 3-D imaging is now available and has the advantage of providing more accurate volume assessment (comparable with MRI) and further detailed valvular evaluation especially prior to surgery (Figures 2D, 2E).

Furthermore, analysis of tissue and blood motion within the heart is performed with Doppler-based technologies. This uses the Doppler equation to assess the tissue or blood velocity by proportionality of velocity with the frequency shift of returning ultrasound. Pulsed Doppler allows accurate blood velocity measurement over time in the cardiac cycle (such as the left ventricular outflow tract (LVOT)), and integrating the velocity time integral (VTI) spectral curve and multiplying by the area of the orifice results in flow volume (such as left ventricular stroke volume = LVOT VTI x LVOT area). Continuous Doppler velocities are depicted as spectral tracing of all velocities along a sampling cursor. This is most useful in measuring peak velocities and gradients across a valve such as for aortic stenosis. The gradient is directly proportional to velocity by the simplified Bernoulli equation [Gradient(mmHg) = $4V^2$ where V= Doppler velocity in m/sec]. Both peak and mean gradients can be determined by measuring the maximal velocity and the velocity time integral. Furthermore, valve area can by calculated using the continuity equation. For example, for the aortic valve (AV), Aortic valve area = (LVOT VTI x LVOT area)/AV VTI. Colour Doppler flow employs multigate pulsed Doppler to portray blood flow overlying the 2-D image. By convention, blue represents blood flowing away from the transducer and red towards the transducer. Lighter colours signify higher velocities and turbulent velocities may have a green hue or a mix of colours due to aliasing. This is useful in detecting valvular stenosis or regurgitation (Figures 2B, 2C), left ventricular outflow obstruction such as in hypertrophic cardiomyopathy and also for shunts. Tissue Doppler imaging is used to assess low-velocity movements

of the myocardium and performing this technique on mitral and tricuspid annular motion correlates to both systolic and diastolic performance of the ventricles.

B. TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography (TOE) allows for excellent visualization of cardiac structures due to the proximity of the oesophagus and the left atrium (Figure 2C). TOE is complementary to TTE with its own strengths and weaknesses. It provides an unobstructed echocardiographic window by avoiding intervening lung and chest wall issues that limit TTE. TOE is relatively contraindicated with esophageal pathology (stenosis or varices), cervical spondylosis or severe respiratory conditions (unless intubated). The patient is asked to fast for at least 6 hours prior to the procedure and a 20-guage intravenous cannula is inserted for administration of medications and contrast if needed. Lidocaine spray is routinely used for topical anesthesia and midazolam +/- fentanyl are used intravenously for moderate sedation. The patient is then intubated with a lubricated probe whilst in the left

Table 2 – Indications for Transoesophageal Echocardiography

Valvular disease, especially prior to cardiac surgery and for prosthetic valve dysfunction
Infective Endocarditis, looking for vegetations and valvular dysfunction severity
Cardiac source of embolism including left atrial appendage or left ventricular thrombus, patent foramen ovale, aortic atheroma or fibroelastomas
Atrial fibrillation, to exclude left atrial appendage thrombus prior to DC cardioversion
Aortic pathology (aneurysm, dissection, atheroma)
Cardiac masses
Congenital heart defects
Intraoperative cardiac monitoring
Guiding structural interventional procedures such as atrial septal defect/patent foramen ovale closure and transcatheter aortic valve implantation
Poor transthoracic images

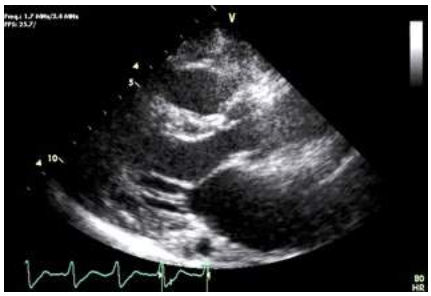


Figure 2A. Transthoracic parasternal long axis 2-D echocardiogram showing incomplete closure of the mitral leaflets due to tethering of both leaflets as a complication of septal myectomy for hypertrophic cardiomyopathy.

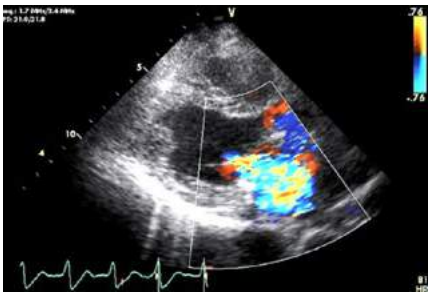


Figure 2B. Transthoracic parasternal long axis 2-D echocardiogram with Colour Doppler showing the severe mitral regurgitation secondary to incomplete closure of the mitral leaflets.

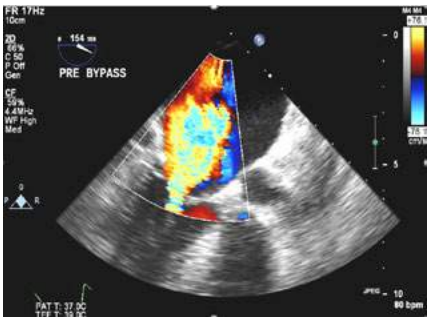


Figure 2C. Transoesophageal 2-D echocardiogram with Colour Doppler showing the severe mitral regurgitation into an enlarged left atrium secondary to incomplete closure of the mitral leaflets. In transoesophageal echocardiography, the top of the picture depicts the left atrium due to its close proximity to the oesophagus where the probe lies.

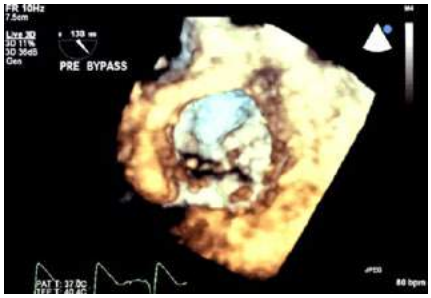


Figure 2D. Transoesophageal 3-D echocardiogram showing the anatomy of the mitral valve with incomplete closure of the mitral leaflets due to significant tethering posterior>anterior leaflets.

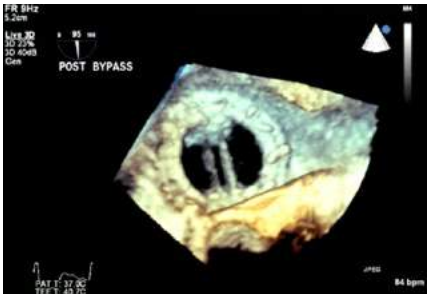


Figure 2E. Transoesophageal 3-D echocardiogram showing the prosthetic mitral valve after mitral valve replacement during surgery.

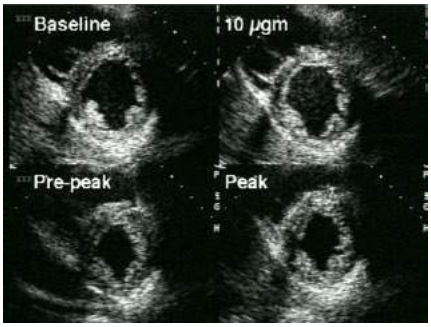


Figure 3. Dobutamine Stress Echocardiography, showing the parasternal short axis images in quad view for direct comparison at rest, low-dose, mid-dose and peak dose dobutamine. There is thickening of the myocardium with a smaller LV cavity with increasing dobutamine dose, which is the normal response to stress.

lateral position and images are obtained from the mid-oesophageal and gastric positions. Contrast in the form of agitated saline is often performed as a bubble study to exclude right to left shunting through a patent foramen ovale. The procedure lasts for about 20 minutes and possible complications are rare but include throat pain, respiratory distress and/or hemodynamic instability due to sedation and esophageal perforation. The major indications for performing a TOE are listed in Table 2.

An interesting case of mitral regurgitation using 2D transthoracic as well as 2D and 3D transoesophageal imaging is shown in Figures 2A-E.

C. STRESS ECHOCARDIOGRAPHY

A stress echocardiogram is a further modality which gives additional information to the clinician. Table 3 lists common indications for stress echocardiography. It is used primarily to detect the presence and extent of coronary artery disease by provoking regional ischemia with resultant wall motion abnormalities. The addition of Doppler permits evaluation of valvular function, pulmonary artery pressure and left ventricular outflow tract gradients. The sensitivity (85%) and specificity (80%) of stress echocardiography for significant coronary artery disease are comparable to MIBI scan and superior to stress ECG. The stress part of the study, which aims to achieve at least 85% of target maximal heart rate, may be done with exercise (treadmill or bike) or with pharmacological stress (dobutamine infusion). Stress echocardiography is particularly important in patients who have abnormal ST segments on ECG at rest (such as left bundle branch block, V-pacing, pre-excitation, left ventricular hypertrophy with strain, digoxin changes) for which a stress ECG would be non-diagnostic. It is also extremely helpful in patients who require a stress test but cannot exercise – in these cases a dobutamine stress echocardiogram is indicated. Dobutamine infusion is performed in five 3 minute stages at 5mcg/kg/min followed by 10, 20, 30 and 40 mcg/kg/min. The addition of 0.5mg iv atropine is sometimes required to reach target heart rate.

Table 3 - Indications for stress echocardiography

Diagnosis of ischemia in patients with chest pain or dyspnea
Determine physiological significance of coronary stenosis prior to revascularization
Risk stratification after myocardial infarction or in asymptomatic patients with prior revascularization (2 years after PCI and 5 years after CABG)
Preoperative risk stratification in patients at increased risk for perioperative events
Evaluation of patients with heart failure or cardiomyopathy for possible underlying ischemic heart disease
Assess physiological significance of valvular lesions, particularly mitral stenosis and regurgitation
Viability testing (looking for hibernating myocardium) using dobutamine stress
To assess patients with low gradient severe aortic stenosis – differentiates true aortic stenosis from pseudo-aortic stenosis in patients with low cardiac output
Evaluation of left ventricular outflow tract obstruction, mitral regurgitation and pulmonary pressures with stress in patient with hypertrophic obstructive cardiomyopathy

Images are taken in 4 standard views – the parasternal long axis, parasternal short axis, apical 4 chamber and apical 2 chamber. These are taken at rest and immediately post-stress in exercise echo and at rest, low-dose, mid-dose and peak dose with dobutamine infusion (Figure 3). Then direct comparison of images is performed. Sometimes, contrast agents are given to enhance the endothelial border for better visualization and more accurate assessment of response of the myocardium to stress. A normal stress echo results in hyperdynamic response of all myocardial segments with increase in ejection fraction and reduction in left ventricular cavity size. The development of new or worsening segmental wall motion with stress suggests the presence of hemodynamically significant coronary artery stenoses supplying the abnormal segment. Features of a high-risk abnormal stress test include decreased left ventricular ejection fraction and/or increase in left ventricular end-systolic volume with stress, extensive ischemia (multiple dysfunctional segments) with stress or ischemia at low workload.

CONCLUSION

In summary, echocardiography is a readily available, portable non-invasive imaging modality to assess cardiac structure and function. In modern day medicine, nearly all patients presenting with cardiac symptoms should be assessed with the help of this extremely versatile tool which no doubt equips the clinician with insight into the diagnosis and management of the patient.

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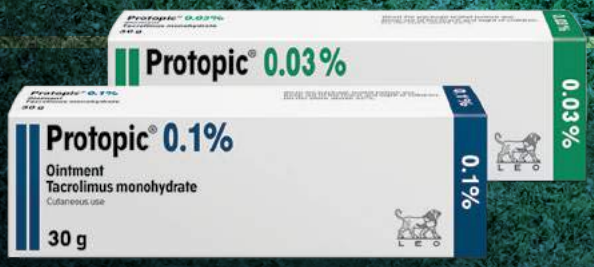

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DR ALFRED GRECH, DR STEPHEN WEST, DR RAMON TONNA

Clinical Relevance of Pharmacoepigenetics

ABSTRACT

Epigenetics – defined as the inheritable changes that are not accompanied by alterations in DNA sequence – is a rapidly growing field and its research is being proposed for implementation into the clinical setting. Indeed, advances in epigenetics and epigenomics (which focuses on the analysis of epigenetic changes across the entire genome) can be applied in pharmacology.

Specifically, its application has given rise to a new specialty called pharmacoepigenetics, which studies the epigenetic basis for the variation between individuals in their drug response. Pharmacoepigenetics can become one of the tools for the personalised medicine approach, with potentially safer treatments and less side-effects on the horizon.

INTRODUCTION

Several research studies have shown that patients displaying similarities in disease expression may produce distinct responses to the same drug treatments. Although factors such as age, body-surface area, disease stage, gender or weight may be partly responsible, personalising treatments based on these factors does not completely tackle this problem. In fact, medical specialists are increasingly shifting in the direction of patient genomic data for selecting optimal treatments in specific scenarios. In addition, a growing body of evidence has revealed that epigenetics also plays a significant role in ascertaining the efficacy and safety of drug treatments in patients.[1]

Developments in epigenomics, including advances made by the Human Epigenome Project, have laid the foundations for the growing field of pharmacoepigenetics. Pharmacoepigenetics originally arose as a discipline to research how epigenetic patterns influence patients' drug responses. However, there is now another development for pharmacoepigenetics: therapeutic epidrugs designed to initiate changes in the epigenome, to reduce the symptoms or progression of a disease for individual patients. Notwithstanding the substantial knowledge gap that exists between our understanding of clinical treatments and epigenetic modifications on drug metabolism mechanisms, pharmacoepigenetics is a developing field with the potential to bridge the gap and be of great utility in personalised medicine.

PHARMACOEPIGENETICS AND HUMAN DISEASES

Underlying the development of effective epigenetic therapies are the epigenetic mechanisms and the proteins involved, including DNA methylation, histone modifications and regulatory miRNA.[2] DNA methylation is closely linked with histone modifications, and their interaction is fundamental in controlling genome functioning by altering chromatin architecture. In addition, a group of miRNAs known as epi-miRNAs can directly target effectors of the epigenetic machinery, including DNA methyltransferases, histone deacetylases (HDACs), and polycomb repressive complex genes. Such epigenetic–miRNA interaction results in a new layer of complexity in gene regulation, opening up new avenues.

In this article, we will discuss briefly how these mechanisms link to diseases such as cancer, heart and neurodegenerative diseases, autism, bipolar disorder, depression and immunological disorders.

Cancer

It is true that, when it comes to the epigenetic aberrations of particular cancers at different steps in tumour development, a lot of work still needs to be carried out. It is also true, however, that there is a general understanding of which modifications lead to irregular gene expression in relation to the different types of cancer. In fact, these epigenetic biomarkers are being applied in the clinic as a tool to first detect cancer and classify the tumour, and then to understand the drug response to treatment.

As an example, the DNA methyltransferase inhibitors azacitidine and decitabine have been approved by FDA for the treatment of patients with acute myeloid leukaemia, chronic myelomonocytic leukaemia and higher-risk myelodysplastic syndromes; the latter being a group of cancers where blood cells from the bone marrow do not mature properly into healthy blood cells.[3,4]

Azacitidine, together with another drug called entinostat, has also been used in clinical trials of non-small-cell lung carcinoma.[5] In this particular study, 4 out of 19 patients had major objective responses to anticancer therapies given directly after epigenetic therapy. Entinostat, a HDAC inhibitor, prevents gene silencing by allowing access to the transcription machinery. Entinostat has also been shown to be a promising treatment for patients with advanced breast cancer.[6]

MiRNA-based therapeutic strategies have also been applied in cancer. For example, a new miRNA drug candidate called RGLS5579 that targets miR-10b has been announced for potential trials in patients diagnosed with glioblastoma multiforme, one of the most aggressive forms of brain cancer.[7]

Heart Disease

In the developed world, mortality and morbidity from cardiovascular diseases (CVDs) represent a large burden to society.[8,9] CVDs such as *atherosclerotic cardiovascular disease*, cardiomyopathy, congenital heart disease, heart failure and hypertensive heart disease are now being tackled as much more multifaceted disorders. Indeed, the epigenetic research in this field is now more prevalent and histone modifications and miRNAs have also been found to have a key role in heart disease.[10]

In 2016, Somanna et al. published the findings of their study which used the HDAC inhibitors Trichostatin A and Mocetinostat to show that targeting HDACs weakens the pro-fibrotic and pro-inflammatory effects of angiotensin (Ang)-II on adult mouse cardiac fibroblasts.[11] In addition, there is an increasing number of publications showing that miRNAs play a significant role in numerous aspects of heart failure. One such study is that by Yang et al. (2019), who found that miRNA-19b-1 reverses ischaemia-induced heart failure by inhibiting the apoptosis of cardiomyocytes.[12] In a different study, Verjans et al. (2019) identified miRNAs as multi-cellular regulators of different processes that cause cardiac disease. Specifically, they characterised formerly undescribed roles of miRNAs in fibrosis, hypertrophy and inflammation, and ascribed novel effects to many well-known miRNAs.[13]

Neurodegenerative Disorders

Brain disorders with a vascular and/or neurodegenerative constituent are a common problem worldwide. One way in which this could be mitigated is through pharmacoepigenetics.

DNA methylation could be restored, for instance, to regenerate the metabolic pathways disturbed by DNA hypomethylation, which is linked with the progression of some of the most widespread neurodegenerative disorders, including Alzheimer's and Parkinson's disease. Indeed, the ability of S-adenosyl-L-methionine and the B vitamins, including folic acid, to restore methylation, together with their brain protective properties, makes them good diet supplements for treating these diseases. Currently, vitamin B6 and folate are proposed for clinical trials to ascertain whether these interventions could possibly decrease cognitive impairment in patients with Alzheimer's disease.[14]

HDAC inhibitors could also restore histone deacetylation, which is a shared feature of numerous neurodegenerative processes. In animal models, several HDAC inhibitors under development offer beneficial effects for cognitive and memory levels of Alzheimer's and Parkinson's diseases. However, only nicotinamide, sodium phenylbutyrate and valproic acid are in clinical trials as epidrugs for treating neurodegeneration.[14,15]

MiRNAs also play a role here. For instance, the overexpression of miR-124[16] and miR-195[17] decreases the levels of the β-amyloid (Aβ) plaques, which are known to cause the neurodegeneration in Alzheimer's disease. In addition, miR-323-3p[18] has been found to decrease neuroinflammation related to Alzheimer's disease. Other non-coding RNAs, such as miR-34b/c, miR-132, and miR-221, are also possible biomarkers and therapeutic targets for Parkinson's disease[14,19].

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is used to describe development disorders caused by a combination of genetic and environmental factors. Recently, the multigenic condition of ASD has been speculated to depend on epigenetic effects[20], although this remains unclear.

For this reason, pharmacoepigenetics in ASD is still in its early stages. While research on epigenetic predictors of drug response is rare in ASD, the data on the development of epidrugs is encouraging. DNA methyltransferase inhibitors have been found to reactivate repressed genes in autism-associated genetic conditions, and more precisely, RNA-therapeutic targeting genes were used to reactivate MeCP2, which is a candidate gene of ASD. In animal studies, HDAC inhibitors have also been shown to enhance cognitive impairment and social behaviour.[21]

Bipolar Disorder

Studies have also been investigating the role of epigenetic mechanisms in bipolar disorder and its treatment. Some of these mechanisms have been shown to be involved in the action of antidepressants, antipsychotics and mood stabilisers used for treating patients with bipolar disorder.[22]

In a paper published in 2015, Backlund et al. investigated whether DNA methylation levels vary between healthy controls and bipolar patients when treated with either lithium or a combination of lithium and valproate, both of which are mood stabilisers. The authors found that lithium in monotherapy was linked to hypomethylation, whereas lithium and valproate displayed a hypermethylated pattern when compared to lithium alone.[23] This suggests that the choice of treatment in bipolar disorder may lead to different levels of DNA methylation. However, more research is necessary to understand its clinical significance. Having said that, these epigenetic biosignatures could eventually revolutionise this field and benefit patients and clinicians alike in the future.

Depression

Major depressive disorder has become a worldwide problem, with more than 50% of those on an initial antidepressant course not showing symptom remission. A genetic basis for the pathophysiology of major depressive

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References: 1. Braithwaite I *et al.* Respir Med 2016; 119:115–121 - **2.** Bardsley G, *et al.* Respir Res 2018; 19:133 - **3.** Relvar Ellipta SmPC - **4.** Svedsater H *et al.* npj Prim Care Resp Med. 2014; 24: 14019 - **5.** Svedsater H *et al.* BMC Pulm Med. 2013; 13:72.

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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, total lactase deficiency or glucose-galactose malabsorption should not use 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 infection, bronchitis, influenza, candidiasis 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**: GlaxoSmithKline (Ireland) Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** January 2019.

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disorder has been strongly indicated in research studies, but despite these breakthroughs, no biomarkers have been satisfactorily validated in treatment responses from clinical practice.[24]

New evidence from both human and animal model studies indicates a prominent role of epigenetic marks, such as histone modifications and DNA methylation, in predicting response to antidepressants. For example, epigenetic modifications of the genes SLC6A4, IL11 and BDNF are demonstrating encouraging signs as biomarkers to predict antidepressant response.[25]

Immunological Disorders

It has been shown that altered epigenetic patterns also play an important role in the development and pathophysiology of immunological disorders, especially autoimmune diseases.[26]

Indeed, HDAC inhibitors have been used in autoimmune disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus and systemic onset juvenile idiopathic arthritis.[27,28] For example, a study revealed a new molecular mechanism by which the HDAC inhibitor Trichostatin A can disturb inflammatory cytokine production in RA synovial cells, suggesting that targeting HDACs may be useful in suppressing inflammation in RA in a clinical setting.[29]

It has also been suggested that DNA methylation contributes to the development of RA, however, with contradictory and unsatisfactory results. Studies have also shown that circulating cell-free methylated DNA in blood offers a non-invasive "liquid biopsy", providing a template for assessing molecular markers of diseases, including RA. Epigenetic therapies controlling autoimmunity may therefore find far-reaching implications for the diagnosis and management of RA.[30]

CONCLUSION

We know that responses to therapeutic treatments are greatly dependent on our individual genomic and epigenomic profiles, and so personalised treatments ideally should be governed by pharmacogenetic and pharmacoepigenetic methods for optimal efficacy. However, because the epigenetic machinery is versatile, manipulations of epigenetic aberrations may lead to drug resistance.

In the emergent field of pharmacoepigenetics, there is a current lack of information regarding the long-term consequences of epidrugs exploiting targets with no real cell specificity. In fact, procedures must first integrate pharmacoepigenetic studies in order to evaluate safety concerns and treatment efficacy in developing drugs and subsequent clinical trials.

Despite recent major strides in the field of pharmacoepigenetics, it is only after further investigation that we will fully understand the role of epigenetic modifications in human health, such that we can harness its potential power for personalised treatment of disease.

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Dr Ian Ellul catches up with the Superintendent of Public Health **Prof. Charmaine Gauci**

Maltese Queen of Hearts

Kintsugi is Japanese art in which broken ceramics are meticulously mended with a lacquer resin mixed with gold or silver. This turns broken objects into magnificent pieces of art. Well, let's hope that this pandemic makes us stronger and even more resilient to change. And who knows? Maybe we will also see more medical students choose public health as career. In the meantime, Dr Ian Ellul catches up with the Superintendent of Public Health Prof. Charmaine Gauci, who is also a Public Health Medicine Consultant, to discuss the current management of Covid-19.

DESCRIBE HOW YOUR FAMILY'S LIFE CHANGED DURING THESE LAST WEEKS SINCE COVID-19 TREADED ON OUR SHORES?

I have been Superintendent of Public Health for the last three and a half years. Long hours have always been characteristic of my work, even in my previous role as Director of Health Promotion and Disease Prevention Directorate within the Superintendence of Public Health. Nonetheless, Covid-19 was a game changer. My hours of work had to stretch even more simply because the workload increased; I have to deal with different teams on a daily basis to arrive at informed decisions. My family feels part of this all and have been fully understanding and supportive. I am grateful for such a blessing.

WHAT ARE YOUR VIEWS ON THE FACT THAT IN THE INITIAL PHASE, HEALTHCARE WORKERS WERE INADVERTENTLY IMPORTING THE DISEASE, AFTER TRAVELLING ABROAD, AND SPREADING IT TO COLLEAGUES?

Everyone has responsibilities. However, one must also understand that during those initial times nobody had a precise foresight of the infection trajectory which Malta would experience; presumably, back then, these healthcare professionals had not envisaged that going for commitments abroad, booked months before, would have resulted in infection and subsequent transmission. In keeping with this, even WHO dragged its feet in declaring Covid-19 as a public health emergency of international concern. I am not here to judge people. My role is to support anyone affected by any means during this pandemic and protect the Maltese nation. Fortunately for us Malta was prepared since we had been expecting this pandemic since December 2019. Our first cases got delayed and so we also managed to gain precious time to learn lessons from what was happening in other countries.

MEDIA HAS RECENTLY REPORTED THAT FIVE DAILY CASES IN MALTA ARE EQUIVALENT TO 600 PATIENTS IN ITALY, CONSIDERING POPULATION SIZE. IS THIS CORRECT?

When comparing statistics, one must factor in the testing capacity. To data, when compared to Italy, Malta's number of tests per capita has been threefold.

Our testing strategy has evolved gradually to become more comprehensive. Initially we tested symptomatic people who returned from abroad, then we included symptomatic people who did not go abroad, afterwards we expanded testing to include other symptoms such as GI-related ones. Finally, we started doing outreaches to industry and to people who have contact with others, so as to maximize the chances of identifying asymptomatic carriers, including healthcare workers.

IN MAY MALTA PLEDGED €400K DURING THE EU-LED TELETHON WHICH RAISED $8BN TO DEVELOP COVID-19 DIAGNOSTICS, TREATMENTS AND VACCINES. DOES THIS GIVE MALTA PREFERENTIAL ACCESS TO THE VACCINE, WHEN AVAILABLE?

Countries did not have any direction on how much money is expected of them. However, obviously Malta pledged that amount to be part of the research framework, and ensure access to the vaccine for our nation when it is marketed.

THE GOVERNMENT IS PROCURING OVER 800 TONNES OF PPE AND NOW WE ALSO HEARD THAT A NUMBER OF LECTURE HALLS IN THE UNIVERSITY OF MALTA'S GATEWAY BUILDING ARE BEING CONVERTED INTO HOSPITAL FACILITIES. ALL THIS IS OCCURRING IN PARALLEL TO EASING OF SANCTIONS. CAN YOU CLARIFY THIS?

The current situation is stable with a small number of cases ebbing and flowing. When one considers the total number of tests done per confirmed case, one realises that currently we have a lower number of positive cases when compared to the period when we started importing them from abroad, back in March. Currently these cases include symptomatic as well as asymptomatic cases, with some cases being identified through contact tracing and enhanced testing.

When we started relaxing measures which involved low and medium-risk areas, we were aware that this could herald an increase in infection transmission rates. Such decisions are always calculated through and through, and are supported by ongoing risk assessments, with mitigation measures to limit

possible increases in cases. We are constantly vigilant and if need be, we will re-introduce the restrictions as necessary. That is why the general population as well as businesses must heed the advice given on social distancing and prevention measures.

We have always been prepared, through effective preparedness plans, a trained workforce, adequate PPE supplies and hospital facilities, and also, through the implementation of the latest evidence-based training protocols.

DURING A RECENT INTERVIEW WITH PROF. SANDRO GALEA, DEAN AT THE BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, US, WE DISCUSSED THE CONCEPT OF THE 'HEALTHIEST GOLDFISH'. REGARDLESS OF THE MEDICINE WE CAN ACCESS OR OUR PERSONAL CHOICES ABOUT HEALTH, THE 'WATER' OF OUR DAILY LIVES - POLITICS, ENVIRONMENT, ECONOMY – ARE EQUALLY IMPORTANT FACTORS THAT SHAPE HEALTH. HOW DO YOU VIEW THE RELATIONSHIP BETWEEN POLITICS AND PUBLIC HEALTH DURING THIS PERIOD?

I strongly believe in good governance. I equally believe that the concept of *common wealth* of a nation and of its citizens should be top agenda of any government. I am a public health medicine specialist which means that I must equate the best interests of the individual person with that of the entire population. This entails considering the social and economic determinants of health. A person can only be healthy and have a good quality of life if one has access to basic education, adequate housing, is employed, has adequate income, and surrounded by a good environment

In this pandemic one could have easily instructed everyone to stay indoors for a year or so until a vaccine is made available. However, is this good governance? Certainly not. The people and the nation as a whole need to move forward and adapt to a new normality, obviously through the implementation of robust risk management plans.

MALTA HAS BEEN A TRAILBLAZER IN MITIGATING THE EFFECTS OF THE PANDEMIC. WERE YOU EXPECTING THIS?

Our decisions have always been backed by fine-grained evidence-based protocols. In keeping with this, we have treaded prudently, with willingness to learn and adapt. Fortunately, our hard-working teams, largely composed of public health specialists, have exceeded expectations in this regard. However, truth be told, we had to implement some pretty hard measures, at times risking backlash … it was not nice to have people telling you that since WWII, Malta has never shut schools. Nonetheless, we took decisions with great responsibility and we have consistently been open to public scrutiny; since the very beginning, we adopted a transparent approach, updating the Maltese population on a daily basis. Public health specialists, health professionals from all entities and other involved sectors were also all over the media to disseminate information.

APART FROM MALTA CAN YOU MENTION ONE OTHER COUNTRY THAT HAS BEEN EFFECTIVE IN MITIGATING THE EFFECTS OF COVID-19?

It is very difficult to compare countries since each has its own unique social fabric. Maltese people are accustomed to visit family or friends on a regular basis, going out on every weekend, etc. This scenario is very different to what is found in e.g. Nordic countries. This means that the mitigation measures implemented by specific countries have affected the social and economic determinants of health to a different degree of others. Thus, a direct comparison is very challenging.

ANY LESSONS LEARNT FROM MISTAKES POSSIBLY DONE IN MALTA DURING THIS PERIOD?

Our Public Health Covid-19 Response Team boasts a flat organization. There are different teams dedicated in the management of the helpline, swabbing, case management, communications, contact tracing, data management and statistics, patient discharge, transition team and epidemic intelligence. We meet frequently to discuss all forms of strategic actions. We also have a central management team as well as a senior advisory team which takes high level decisions. Data is collated in a central repository - Go.Data - which is an outbreak investigation tool manged by WHO and utilised for field data collection during public health emergencies. It was initially used for Ebola, and Malta, together with other countries, has adapted it for Covid-19. All this gives us peace of mind that any possible shortcomings which are identified, are handled responsibly and in a timely manner by our response team.

YOUR MOST DIFFICULT MOMENT DURING THIS PERIOD?

Giving news relating to deaths. Deaths which are avoidable are ultimately always difficult to confront.

COVID-19 CERTAINLY PROVIDED TAILWIND FOR TELEMEDICINE AND ECME. WHAT ARE YOUR VIEWS ON THIS?

I agree perfectly. In keeping with what you are saying, primary care physicians follow Covid-19 cases that remain in community through telemedicine. Also, speaking for myself, I have days which are jam-packed with online meetings, back-to-back. How could this be possible if I had to travel back and forth between meeting venues? Although I miss human interaction, I strongly believe that some concepts are here to stay.

HOW DO YOU ENVISAGE YOURSELF IN 10 YEARS TIME?

I love what I do. My career revolves around the wide aspect of public health, and specialized further in infectious diseases epidemiology where I also read a PhD on this subject. Nonetheless, I will embrace any path which life chooses for me.

I READ THE SYNAPSE MEDICAL JOURNAL BECAUSE …

The Synapse is a platform that I access regularly as I consider it as a reliable source of evidence-based information. I have the peace of mind that I can use The Synapse in my work as public health specialist and share its content with colleagues.

Stay Healthy & Safe!

DR PATRICK CHOUEIRY

A Brief Review on the Growing Concept of Nutraceuticals

While all agree that the term "nutraceutical" comes from the association of the words nutrition and pharmaceuticals, it was actually coined in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ.[1] According to DeFelice, any food or part of food that would provide health benefits or prevent and even treat any disease, mainly chronic ones, would be termed nutraceutical. Since then, the word became commonly used to include any food, plants, herbs, vitamins, minerals, proteins or other ingredients like pre- or probiotics, that would have the aforementioned benefits by targeting a substance insufficiency in the body or by simply supplementing and increasing the total daily intake of a constituent, metabolite, extract or the combination of these ingredients.[2] However, although nutraceuticals would become largely regulated by the different health bodies in various countries like the US Food and Drug Administration, European Food Safety Authority (EFSA), the Chinese SFDA, the Indian FSSA and others, the word nutraceutical remains with no regulation definition.[3]

REGULATORY FRAMEWORK

For nutraceuticals manufactured by European nutraceutical companies, the manufacturing, marketing and selling of end products are mainly overseen by the EFSA,[4] which also evaluates the claims associated with these products through the Register of Nutrition and Health Claims.[5] Through its focal points, the EFSA cooperates with national food safety authorities that give EFSA strategic advice on scientific issues relating to nutraceuticals and food supplements and are the most important contributors of experts to EFSA. For Malta, the national regulator is the Maltese Competition and Consumer Affairs Authority.[6] Inclusion of a new claim would require further detailed scientific testing done by the manufacturer and reviewed by EFSA. Since the health claims on product labels need to be approved by EFSA, this gives increased credibility to EU produced food supplements and nutraceuticals.[7]

SIZE OF MARKET

Despite the tough EU regulations on nutraceuticals, these didn't negatively affect the growth of the nutraceuticals market worldwide. Indeed, and as per the Euromonitor 2010 figures, it was projected that the value of the annual global nutraceuticals market would reach US$250 billion by 2018 with the global nutraceuticals market by country/regional share split being as follows: Europe 14%, Japan 22%, USA 30% and the rest of the World 34%.[8]. In fact, the actual 2018 market size of nutraceuticals accounted for US$379 billion with an expected large growth to reach US$734 billion in 2026.[9]

While until recently it was perceived that pharmaceuticals are mostly medications used to treat diseases, and nutraceuticals substances used to prevent diseases,[10] this distinction between pharmaceuticals and nutraceuticals has been shown to be incorrect and even erroneous.

Pharmaceuticals are compounds which undergo thorough testing. The results form part of a dossier which is evaluated by regulatory authorities and if authorised, the pharmaceutical company benefits from patent protection for that product. Though not considered strictly pharmaceutical, herbal medicinal products are also regulated products. Herbal medicinal products are either granted marketing authorization with a well-established use or are registered as a traditional herbal medicinal product. Safety and efficacy data is mandatory and is derived from bibliographic data or tests carried out by the manufacturer. On the other hand nutraceuticals do not need the same extent of testing.[4]

EFFICACY AND SAFETY OF NUTRACEUTICALS

Currently, nutraceuticals are receiving a lot of interest due to their therapeutic promises that are being increasingly documented through clinical studies and more so due to their relatively better safety profile in comparison to pharmaceuticals. However one must add that there are specific natural products that have a very narrow therapeutic window. In this case, the safety issue is linked to the long-standing use of these products with respect to pharmaceuticals.

Nutraceutical and pharmaceutical companies are aware of the increased interest by the general population in nutraceuticals due to the benefits associated with them. Whenever used for an insufficiency or deficiency in a

vitamin, mineral or other vital molecule, most nutraceuticals also possess multiple therapeutic benefits apart from their disease prevention properties.[11]

To illustrate the importance of this relatively new healthcare industry, international exhibitions and fairs are held to allow exhibitors, mainly nutraceuticals and food supplements companies, to show the benefits of their products. Visitors of these fora include healthcare professionals from different backgrounds as well as other professionals interested in the development and growth of the nutraceutical business. Vitafoods Europe is one of the most prominent annual event where the nutraceutical industry comes together to innovate, connect with business leaders and find effective solutions in the sole interest of the individual's health. In 2019 Vitafoods gathered more than 1,250 exhibitors, 25,000 visitors and had over 110 participating countries.[12]

The list of nutraceuticals is constantly shaping up. Products, molecules and ingredients are being added or changed incessantly according to the needs of the growing market, opinion of healthcare professionals, feedback from consumers and results on efficacy and safety from ongoing researches. The safety of these products stem from the results of research and clinical trials.[13]

Nutraceuticals are believed to be effective against a plethora of diseases and disorders e.g. cardiovascular, obesity, diabetes, cancer, stress, mental and neurological diseases, hormonal disturbances, women's health disorders, respiratory disorders; they may also function as immuno-modulators, e.g probiotics.[13] While the mechanism of action of nutraceuticals is not fully understood, it is postulated that they are involved in a wide variety of biological processes, including the activation of signal transduction pathways, gene expression, cell proliferation, differentiation and preservation of mitochondrial integrity, and proliferation of human hematopoietic precursors. Working as antioxidants and improving antioxidant defenses is a widely accepted way of action given that reactive oxygen species and oxidative stress are more and more implicated in the etiology of many diseases including atherosclerosis, other cardiovascular diseases and cancer.[10,13]

MANUFACTURING AND IMPORTANCE OF FORMULATION

The manufacturing process poses various challenges, including *stability testing*. The formulation used for specific minerals or ingredients, strains of probiotics and the right mixing of compatible ingredients that would not antagonize each other or decrease their bioavailability or stability are all important considerations.

The importance of the *formulation* development of two commonly available minerals, iron and magnesium, is illustrated below. Because of their low solubility, iron and magnesium are poorly absorbed from the intestine. To enhance their bioavailability, ascorbic acid may be included. While companies offer different nutraceuticals claiming to be superior in managing a condition without any side-effects, studies have shown that specific formulations ensure the best bioavailability, hence efficacy, with the least side-effects. One such formulation is the bisglycinate chelate which is made of two molecules of glycine that are chelated to mineral salts such as iron or magnesium. The mineral-bisglycinate complex is hence readily absorbed in the gastrointestinal tract without being affected by gastric or intestinal pH. It is also minimally affected by the concomitant use of other minerals, and food intake including phytic acid-rich food, thus mimicking the absorption of amino acids from the gut.[14-16]

Like with other bisglycinate minerals, magnesium has been shown to have a better bioavailability than other forms of magnesium especially magnesium oxide.[17] The chelate forms of minerals are reported to have the highest absorption and bioavailability making it one of the most efficacious forms for supplementation (Table 1).[18]

Table 1: Benefits of the mineral-bisglycinate complex[18]

Characteristic of the molecular complex	Physiological significance
Stability (even in the stomach)	Lower interaction with food absorption inhibitors like phytates and oxalates; less interaction with other nutrients
Absence of electric charge (neutral molecule. The glycine molecules wrap the mineral)	Fewer gastro-intestinal side-effects because of lack of dissociation of the mineral; increased tolerability and safety
Smaller molecular size	No need for digestive processes prior to absorption; intact absorption through intestinal epithelial cells

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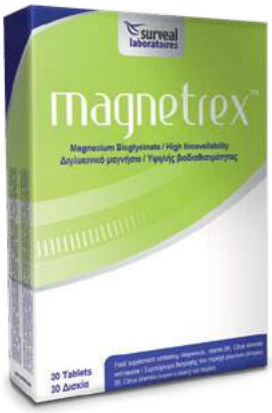

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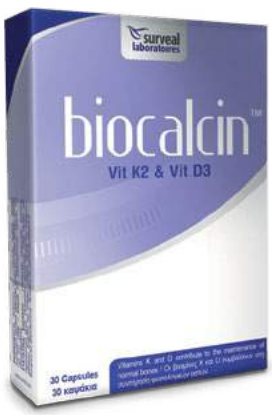

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What about the right recipe? When mixing multiple ingredients in a tablet, capsule or any other form, these must be compatible. Nutrients can be ingested as coated tablets, soft gels, capsules, sachets, effervescent tablets, chewables, dissolvable films, nutrition bars, etc. While some minerals like calcium are best delivered in tablet form, co-enzyme Q10 or lycopene are best preserved when delivered in a soft gel capsule. In the latter case their bioavailability is significantly improved since liquid matrix ingredients are designed to solubilize rapidly even for poorly soluble molecules.[19,20]

Incompatibility of products mixed together not only may lead to physical instability of the formulation like discoloration, breaking, and formation of lumps, but also antagonism among active ingredients or simply not have the required synergistic effect. A good example of mixing compatible ingredients is the case of vitamin K_2 - also known as menaquinone - and vitamin D. This combination is used to help maintain healthy bones. These two products exert synergistic effects on bone metabolism. Vitamin D, also known as 1,25(OH) D_3 is known to promote expression, transcription and translation of osteocalcin (OC) gene. OC is secreted by osteoblasts and activated OC binds to calcium ions and hydroxyapatite crystals allowing good bone mineralization.[21] On another hand, vitamin K_2 stimulates Matrix Gla protein (MGP), an extensively studied extrahepatic Gla protein that is synthetized by chondrocytes and vascular smooth muscle cells. Findings in both animal and human studies suggest that after being carboxylated, hence activated, MGP inhibits the calcification of arteries and cartilage, while facilitating normal bone metabolism.[22] This finding has been translated clinically into improved aortic and carotid elasticity that could be explained by a reduced vascular calcification following long term vitamin K_2 administration to post-menopausal women.[23]

Finally, this fast growing non-pharmaceuticals sector is witnessing better acceptance from consumers as well as healthcare professionals. All this is based on stricter manufacturing requirements like ISO standards and GMP certification (currently this is voluntary), better knowledge about the mode of action of nutraceuticals, and finally more clinical research that shows efficacy and safety.

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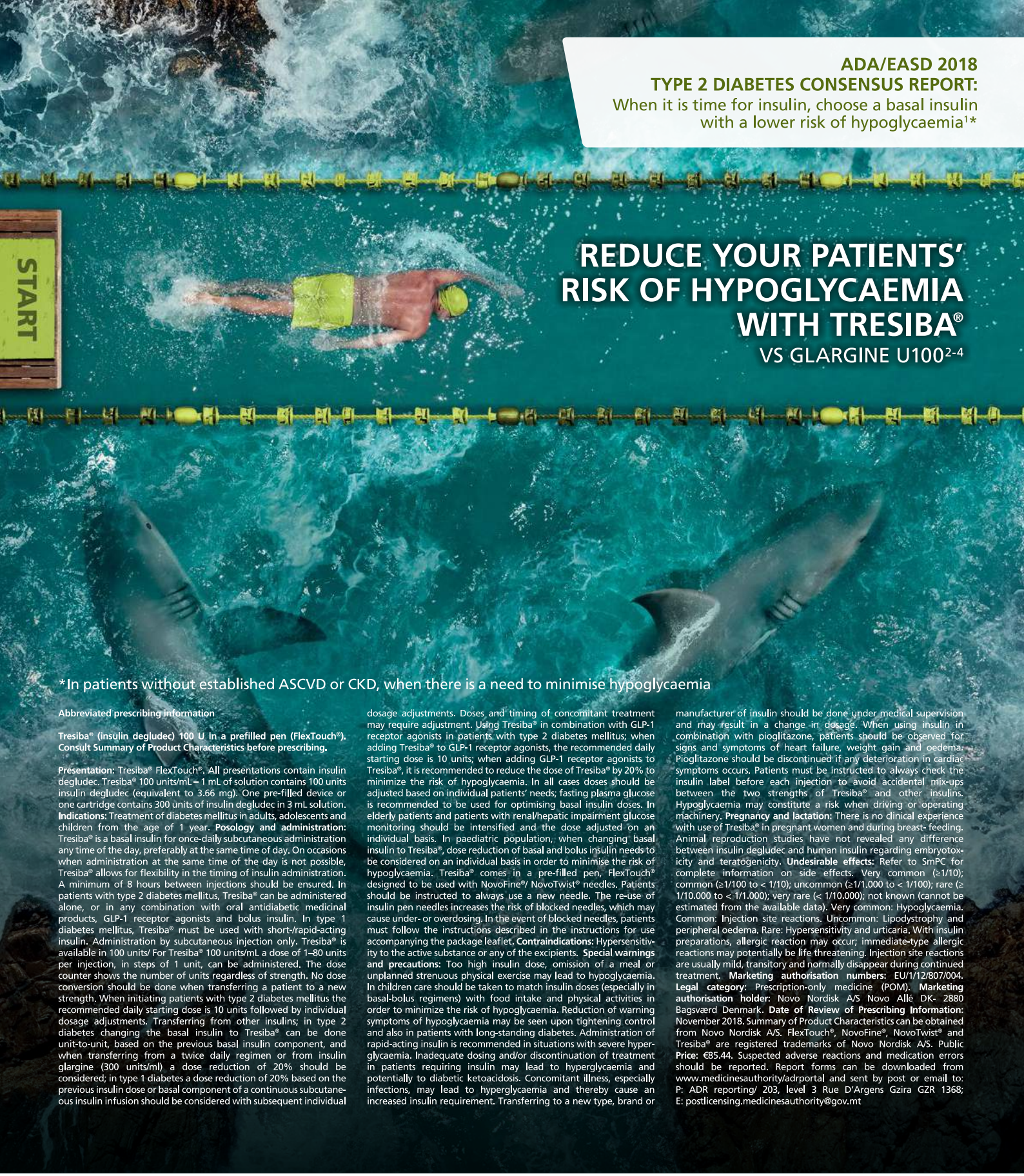


ADA/EASD 2018
TYPE 2 DIABETES CONSENSUS REPORT:
When it is time for insulin, choose a basal insulin with a lower risk of hypoglycaemia[1]*

REDUCE YOUR PATIENTS' RISK OF HYPOGLYCAEMIA WITH TRESIBA®

VS GLARGINE U100[2-4]

*In patients without established ASCVD or CKD, when there is a need to minimise hypoglycaemia

Abbreviated prescribing information

Tresiba® (insulin degludec) 100 U in a prefilled pen (FlexTouch®). Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device or one cartridge contains 300 units of insulin degludec in 3 mL solution. **Indications:** Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. **Posology and administration:** Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/ For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. The dose counter shows the number of units regardless of strength. No dose conversion should be done when transferring a patient to a new strength. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units followed by individual dosage adjustments. Transferring from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component, and when transferring from a twice daily regimen or from insulin glargine (300 units/ml) a dose reduction of 20% should be considered; in type 1 diabetes a dose reduction of 20% based on the previous insulin dose or basal component of a continuous subcutaneous insulin infusion should be considered with subsequent individual dosage adjustments. Doses and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus; when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia. Tresiba® comes in a pre-filled pen, FlexTouch® designed to be used with NovoFine®/ NovoTwist® needles. Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. **Pregnancy and lactation:** There is no clinical experience with use of Tresiba® in pregnant women and during breast- feeding. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. **Undesirable effects:** Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment. **Marketing authorisation numbers:** EU/1/12/807/004. **Legal category:** Prescription-only medicine (POM). **Marketing authorisation holder:** Novo Nordisk A/S Novo Allé DK- 2880 Bagsværd Denmark. **Date of Review of Prescribing Information:** November 2018. Summary of Product Characteristics can be obtained from Novo Nordisk A/S. FlexTouch®, NovoFine®, NovoTwist® and Tresiba® are registered trademarks of Novo Nordisk A/S. **Public Price:** €85.44. Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from www.medicinesauthority/adrportal and sent by post or email to: P: ADR reporting/ 203, level 3 Rue D'Argens Gzira GZR 1368; E: postlicensing.medicinesauthority@gov.mt

IT20TSM00010

Contact Petra Spiteri (Novo Nordisk Key Account Coordinator) on pspiteri@charlesdegiorgio.com for further information.

TRESIBA®
insulin degludec [rDNA origin] injection

The 'New Psychoactive Substances'

The Current Situation on the Maltese Islands from the Laboratory Point of View

1. INTRODUCTION

One of the worst revolutions in illicit drug misuse took place with the development of synthetic drugs. These are drugs that are created using man-made chemicals rather than natural ingredients. Such drugs are not a new phenomenon and have been around since the 1960s when *d-lysergic acid* (LSD) became popular. This was followed by the growing popularity of Ecstasy or MDMA (*3,4-methylenedioxymethamphetamine*) some 20 years later, in the 1980s. These are just two of the many synthetic drugs which exist and, in a way, these first synthetic drugs of misuse can be considered as a prelude to the hundreds of new synthetic drugs that would surface in the years which followed.

Despite being known also as 'designer drugs', 'herbal highs', 'bath salts', and 'legal highs', the preferred term as adopted by the European Community in 2005 is 'new psychoactive substances' (NPSs). They are defined as 'Narcotic or psychotropic drugs that are not scheduled under the United Nations 1961 or 1971 Conventions, but which may pose a threat to public health comparable to scheduled substances'. The word 'new' is not because these are newly synthesised substances, since nearly all of the substances encountered were first synthesised years ago, but merely refers to being newly misused. Their aim is to mimic the effects of the 'traditional' drugs such as cannabis, heroin and cocaine and can be distinguished from the 'traditional' drugs of misuse because, with some exceptions, NPSs have no history of medical use. These substances are also frequently labelled as 'not for human consumption' to try and elude customs drug controls.

2. CURRENT SITUATION ON THE MALTESE ISLANDS

The illicit drug situation has gone through a lot of changes during the past 20 years, not only on the Maltese Islands but also worldwide (Figure 1). This because, 20 years ago, drugs were 'simpler', less potent, and relatively easier to identify. Back then, brown powder was usually heroin, white powder usually cocaine, while green leaves were cannabis, and pills were ecstasy. However today with the phenomena of the new psychoactive substances, this is no longer the case. The brown powder is not always heroin, and neither is the white powder always cocaine. Even green leaves and pills cannot be taken for granted that they are cannabis and ecstasy respectively. NPSs are being sold as alternatives to 'traditional' drugs or sometimes mixed with 'traditional' drugs, therefore not only causing challenges analytically but also to first responders, who may not know the identity of the drug at the scene of the crime.

Figure 2 depicts the current situation on the Maltese Islands. There are currently 2 major types of synthetics we are seeing. These are the ***synthetic cannabinoids*** which mimic the effect of cannabis and the ***synthetic cathinones*** which mimic the effect of cocaine and ecstasy, with the former being more predominant. They consist of 100s of different man-made chemicals.

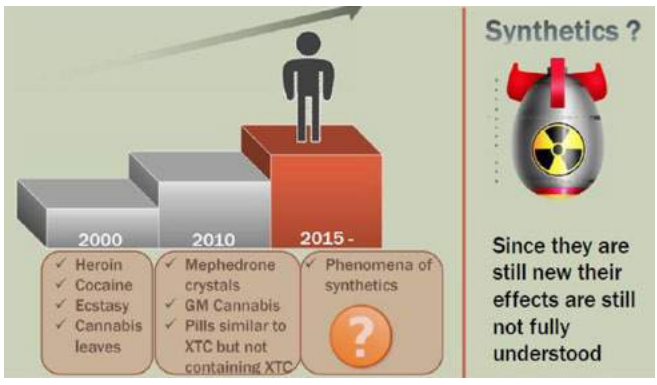


Figure 1 – The trend of illicit drug misuse as seen from the Laboratory. GM – Genetically Modified.

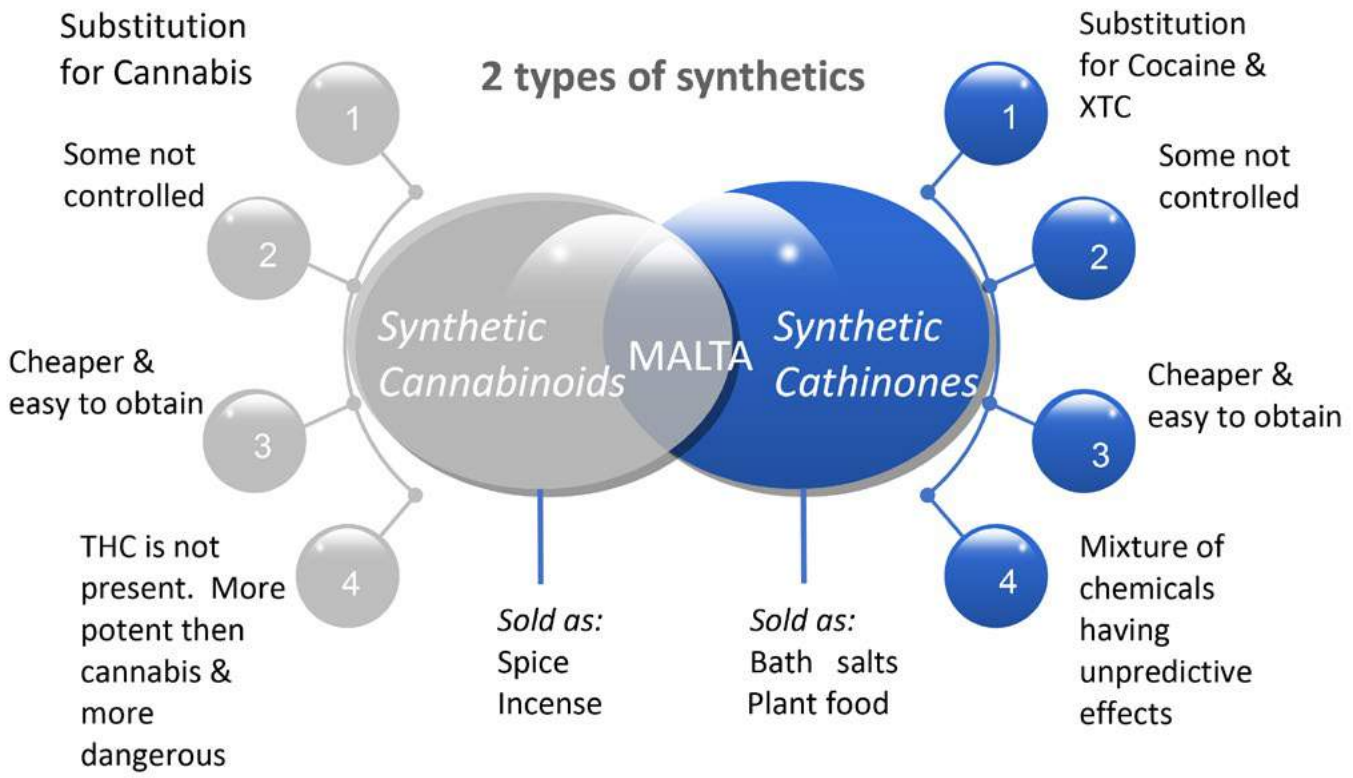


Figure 2 – The current situation on the Maltese Islands.

Synthetic cannabinoids appear as green herbal material (Figure 3). The green herbal material is made up of dried plant material and chopped up herbs in a mixture of colours including beige, red and brown. The active ingredients are synthetic chemicals (the cannabinoids) that are then sprayed onto the plant material. Like cannabis, synthetic cannabinoids are typically smoked.

On the contrary, synthetic cathinones usually appear as white or brown crystal-like powder (Figure 3). Like the drugs they mimic, synthetic cathinones are typically snorted, smoked or injected. Both synthetic cannabinoids and synthetic cathinones can kill.

Another group of NPSs whose appearance to date has been limited on the Maltese Islands are the ***Synthetic Opioids***. These mimic the effects of heroin and are usually added to heroin. Synthetic opioids include the fentanyls which is the most well-known group (Figure 4). Although this class has an important and well-documented therapeutic role - it has analgesic and sedative effects and is used in the management of severe pain and in anaesthesia - misuse can lead to life-threatening adverse effects and acute toxicity. The fentanyls are 50 times more potent then heroin while carfentanyl (licensed for veterinary use on large animals) is 5,000 times more potent then heroin. As one can imagine heroin laced with such compounds would have severe consequences on the user and death can easily result from such ingestion.

Figure 3 – A typical sample of a synthetic cannabinoid (left) and a sample of synthetic cathinone (right). Photos courtesy of the Department of Chemistry, Faculty of Science, University of Malta.

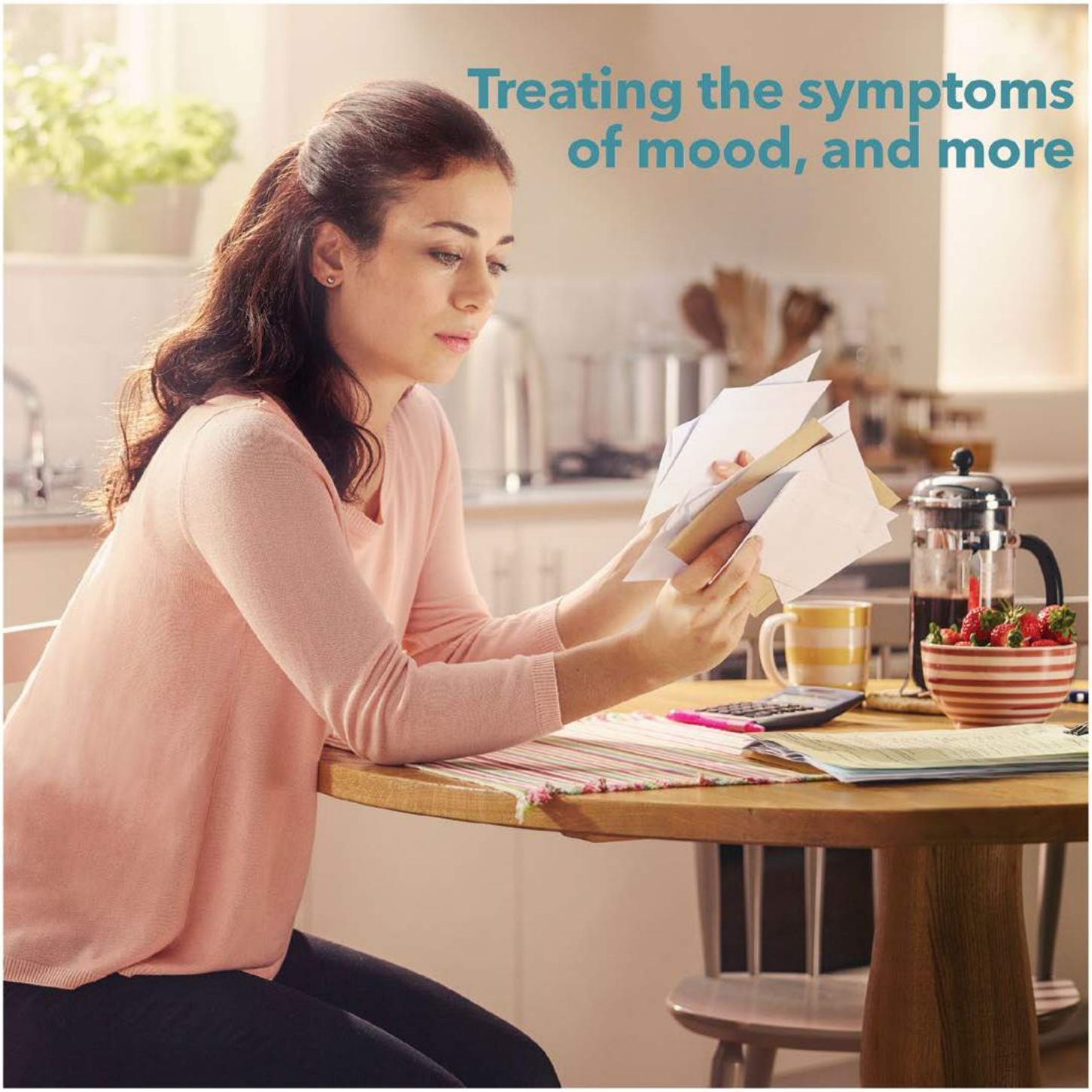
3. WHY ARE THEY SO DANGEROUS?

First of all, when dealing with NPSs, one must keep in mind that these are (1) man-made chemicals and (2) their effects on the human body are still not completely understood.

Synthetic cannabinoids are generally much more harmful than plant-based cannabis. Adverse reactions to synthetic cannabinoids have been reported including deaths whereas adverse reactions to natural cannabis are usually not lethal.

Synthetic cathinones are psychostimulants whose risks are similar to those of cocaine and ecstasy but are much more toxic. The media has often reported instances of bizarre behaviour by someone who has taken synthetic cathinones. This is a rare and uncommon side-effect known as *excited delirium*.

Another reason these new NPSs are dangerous is because the user never knows what he is taking. Unless tested, today you never know whether brown powder is laced with fentanyl or white powder is purely a synthetic,



BRINTELLIX ABRIDGED PRESCRIBING INFORMATION

Please refer to the full Summary of Product Characteristics (SPC) before prescribing, particularly in relation to side effects, precautions and contraindications.
Presentation: Tablets containing 5, 10 or 20mg of vortioxetine (as the hydrobromide). **Indications:** Treatment of major depressive episodes in adults. **Dosage:** 10mg once daily. Dose may be increased to a maximum of 20mg daily or reduced to 5mg if necessary. After depressive symptoms resolve, treatment for at least 6 months is recommended. ***Elderly (≥65 years):*** Initial dosage is 5mg once daily. Caution advised if using doses above 10mg daily as data are limited. ***Children and adolescents (<18 years):*** Not recommended as safety and efficacy not established. ***Cytochrome P450 inhibitors and inducers:*** Consider a dose reduction of vortioxetine if a strong CYP2D6 inhibitor is added. Consider a dose adjustment if a broad CYP450 inducer is added to treatment. ***Renal and Hepatic impairment:*** Given that subjects with renal or hepatic impairment are vulnerable and given that the data on the use of Brintellix in these subpopulations are limited, caution should be exercised when treating these patients. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. Concomitant use with non-selective, monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors (e.g. moclobemide). **Fertility, pregnancy and lactation:** Do not use in pregnancy unless clinically necessary. Limited data on the use of vortioxetine in pregnant women. Animal studies have shown reproductive toxicity. Use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). It is expected that vortioxetine will be excreted into human milk, and a risk to the suckling child cannot be excluded. ***Fertility:*** Animal data showed no effect on fertility, sperm quality or mating performance. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far. **Precautions:** Use caution when driving a car or operating machinery. Closely supervise patients, especially those at high risk, for suicide-related behaviours during first few weeks of treatment and during dose changes. Use with caution in patients: at risk of hyponatraemia; with a history of mania/hypomania; undergoing ECT; with unstable epilepsy (discontinue if seizures begin for the first time or increase in frequency); with bleeding tendencies/disorders, taking anticoagulants or medicines affecting platelet function; in patients on lithium or tryptophan. Monitor patients for appearance of serotonin syndrome or neuroleptic malignant syndrome and discontinue if occurs. **Adverse events:** Adverse reactions were usually mild or moderate, transient and occurred within the first two weeks of treatment. The following adverse events were reported: Very common (>1/10 patients); nausea. Common (>1/100 <1/10); abnormal dreams, dizziness, diarrhoea, constipation, vomiting, pruritis, including generalised pruritis. Prescribers should consult the full SPC in relation to other side effects.

Legal Category: POM. Local Presentation: 28 tablet pack: 5mg, 10mg, 20mg. **Marketing Authorisation Holder:** H.Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark.
Marketing Authorisation Number: 5mg EU/1/13/891/002, 10mg EU/1/13/891/010, 20mg EU/1/13/891/028

Full prescribing information is available on request from the local representative agent of Lundbeck in Malta: Charles de Giorgio Ltd. Triq Kan. K. Pirotta B'Kara, BKR 1114 Malta. Tel: +356 25600 500

Date of preparation: April 2020

Lundbeck

Brintellix® vortioxetine

Brintellix is indicated for the treatment of major depressive episodes in adults.[1]
1. Brintellix Summary of Product Characteristics.

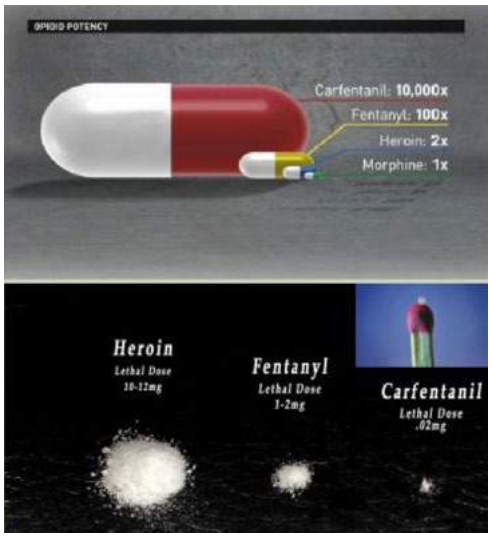


Figure 4 – The potency of the 'traditional' drug heroin compared to the NPSs Fentanyl and Carfentanyl.

and neither do you know whether the green herbal grass has been sprayed with a synthetic cannabinoid which can be lethal.

One very common question that is asked is "if they are so dangerous, why do people still take them?" Well simply put, the reasons include:

- They are readily available
- They are cheaper than 'traditional' drugs
- People may use NPSs since they can more easily avoid detection – at the moment frontline tests do not detect most of the new synthetics, and
- People may just take NPSs accidentally thinking they are taking some other drug instead.

4.WHAT TO LOOK OUT FOR?

Since synthetic cathinones and synthetic cannabinoids are usually purchased over the internet, as healthcare professionals one should be on the look-out for any strange activity reported by patients at home. In keeping with this one should also be aware of common street names of synthetic cathinones, including *Ivory Wave, Vanilla Sky, Cloud 9, White Lighting* and *meow-meow*. These packets usually arrive through the post from China (unless they are stopped by Customs) and sold in the form of 200mg and 500mg packets (Figure 3). The packets often contain a note declaring that the contents are "not for human consumption". This is included in the label with a view to circumvent criminal proceedings against the distributor in specific countries.

Synthetic cannabinoids also come from China in packets usually sold as *Spice* or *Incense*. The packets may also contain a sweet odour since a fragrance such as vanilla, blueberry or strawberry is also added to the green grass.

5. HANDLING

Taking drugs has always been dangerous; however with the introduction of the new synthetics, the user is playing a dangerous game of Russian roulette. Whereas before only one bullet was loaded in the chamber, these days you have 2 bullets loaded in the same chamber. The new synthetics have complicated both the symptoms and the treatment. Prevention and Education are the best antidote.

Whether a police officer, a nurse or a doctor, as a first responder all should take great care when handling unknown powders. Several European Agencies have issued out educational pamphlets directed to first responders, most notably on fentanyl. A similar pamphlet was also issued out by the Forensic Drug Analysis Laboratory located at the Department of Chemistry, University of Malta, to increase the awareness of Fentanyl before it reaches our shore (Figure 5).

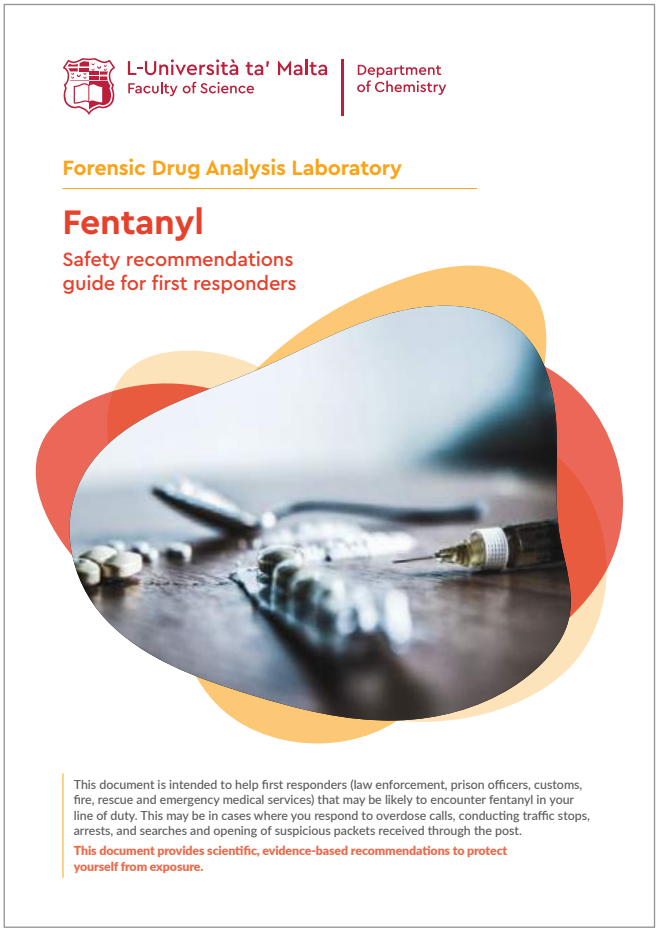
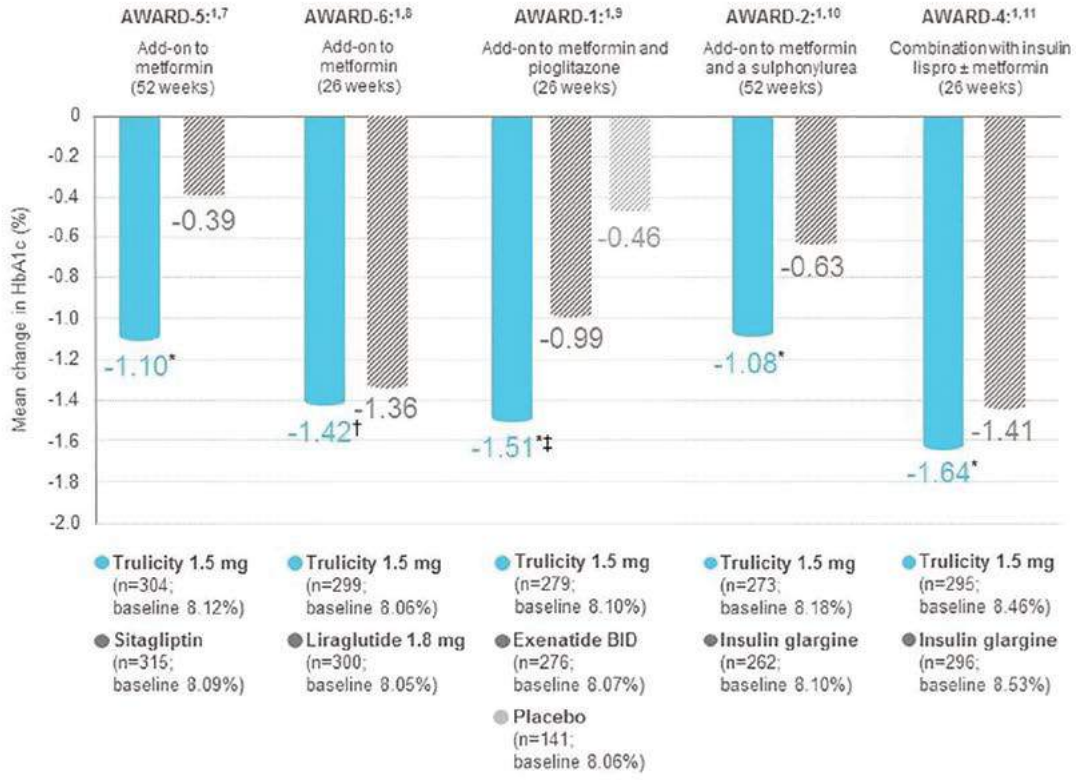


Figure 5 – The front page of the pamphlet, Fentanyl – Safety recommendations guide for first responders.

trulicity
dulaglutide injection once weekly
0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity® provided significant HbA1c reduction in 6 head-to-head clinical trials [1-7]



Trulicity® Ready-to-use pen:

- No reconstitution or priming required
- Preattached, hidden needle
- Each pen contains 1 dose of Trulicity
- Automatic dose delivery; no need to manually pierce skin with needle

Indication: Trulicity is indicated in adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control as:

- **Monotherapy** when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- **Add-on therapy** in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Important notice: Information prepared is for healthcare providers only. Trulicity is a Prescription Only Medicine (POM) Before prescribing Trulicity you are kindly asked to read full Summary of Product Characteristics (SPC). More detailed information about Trulicity and last revision of text SPC are available from https://www.ema.europa.eu/en/documents/product-information/trulicity-epar-product-information_en.pdf. If you wish to report an adverse event (side effect) or product complaint with a Lilly product please call 25600500 or email ccalleja@charlesdegiorgio.com

Charles de Giorgio Ltd – Triq Kan. K. Pirotta – B'Kara< BKR1114 - Malta

Lilly

DR PIERRE VASSALLO

Venous Thromboembolism

DEFINITION

Venous thromboembolism (VTE) is an umbrella term that includes deep venous thrombosis (DVT) and pulmonary embolism (PE).

INTRODUCTION

VTE is a significant cause of morbidity and mortality. It is the third most common cardiovascular condition worldwide following myocardial infarction and stroke.[1] The 30-day mortality rates for patients with DVT and PE are 3% and 31% respectively.[2]

VTE may be isolated (no identifiable cause) or may be secondary to a considerable number of conditions that lead to a hypercoagulable state. The clinical history and an understanding of the risk factors for VTE may point to an underlying cause.

Conversely, knowledge of the predisposing factors may help detect subtle VTE and its complications on ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) studies.[3]

Multimodality imaging (US, CT and MRI) allows early detection of VTE and helps to identify its cause and any associated complications. It is also valuable to monitor the effects of treatment.

CAUSES

Virchow's triad describes the three broad categories of factors, which, in isolation or combined, contribute to an increased risk for venous thrombosis (Fig 1).[2] Venous stasis, damage to the vascular endothelium and conditions leading to hypercoagulable states all increase the likelihood of thrombosis.

Many conditions influence more than one of these mechanisms to increase the risk of thrombosis. The link between hypercoagulable states and malignancy has been well established for most types of malignancy. Some malignancies invade vessels and hence cause endothelial damage; in this group of tumours, the most notable are renal cell cancer, hepatocellular carcinoma, adrenal cortical cancer and non-hyperfunctioning pancreatic neuroendocrine tumours. Tumours may also lead to vascular compression and venous stasis, further increasing the likelihood of thrombosis.

However, the main mechanism that causes VTE in patients suffering from cancer occurs through a stimulation of an inflammatory reaction, which in turn upregulates the coagulation cascade while downregulating the anticoagulative pathways.[2]

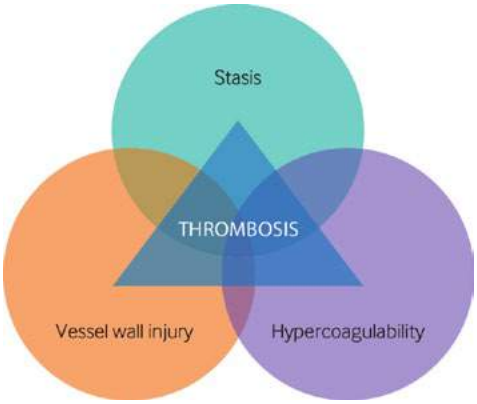


Figure 1. Virchow's Triad outlines the mechanisms that predispose to venous thrombosis.

Infections and major trauma can also increase the risk of VTE provoked by inflammatory responses that influence the coagulative/anticoagulative pathways.[2]

Venous stasis may be the result of prolonged immobilisation and extrinsic vascular compression, such as by enlarged lymph nodes.[4] This can cause direct endothelial damage and hypoxia that can stimulate aggregation of platelets and leukocytes.[5]

Some genetic conditions such as factor V Leiden mutation or deficiencies in protein S, protein C or antithrombin alter distribution of clotting factors in the blood thereby inducing hypercoagulable states (thrombophilia).[6]

Additional risk factors for VTE include major surgery/trauma, orthopaedic injury, oral contraceptive medication, obesity and older age.[3]

DETECTION OF VTE

Ultrasound

Ultrasound is primarily used for detection of peripheral venous thrombosis, where acute thrombus can be visualised directly as hypoechoic tissue expanding the vein, absent compressibility of the vein by the examining ultrasound probe, and abnormal or absent blood flow on Doppler imaging (Fig 2).

The above technique can be used to evaluate the deep lower limb veins, which include the common, superficial and deep femoral and popliteal veins as well as the greater and lesser saphenous veins. The technique is not reliable for detecting thrombosis in deep veins below the mid-calf. In those patients with symptoms that are suspicious for

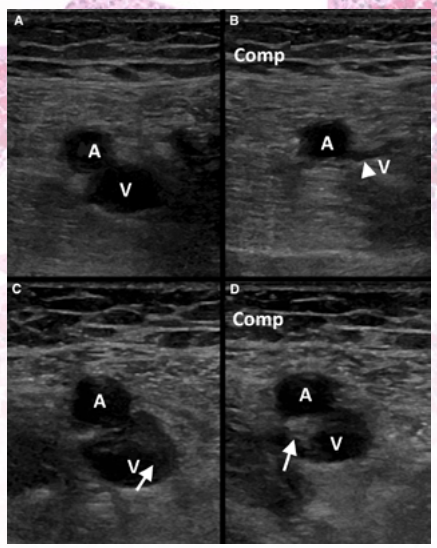


Figure 2. a and b. Normal popliteal vein without (a) and with (b) compression: Note that the vein (V) collapses (arrowhead in b) on compression by the ultrasound probe. c and d. Thrombosed of the popliteal vein without (c) and with (d) compression: Vein (V) does not collapse on compression. The thrombus (arrow in c and d) is easily seen. A is the popliteal artery.

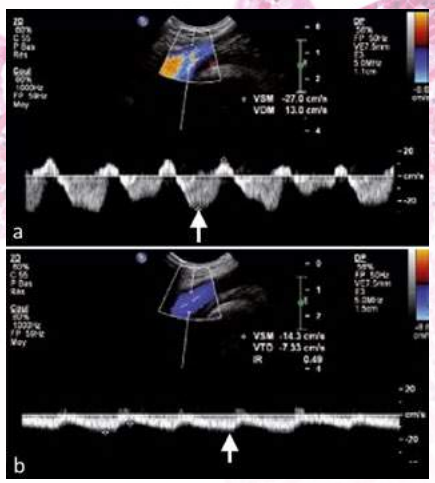


Figure 3. a. Longitudinal triplex doppler scan of the left common femoral vein shows normal phasic flow that fluctuates with respiration. b. On the longitudinal triplex doppler scan of the right common femoral vein, marked dampening of the flow phasicity is noted due to common iliac vein thrombosis. A triplex doppler scan is a scanning mode that delivers a greyscale image with colour and spectral doppler images simultaneously in real-time.

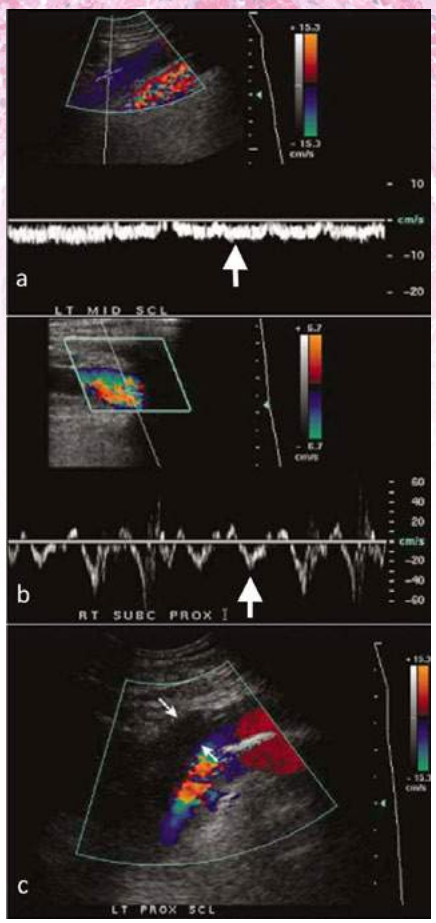


Figure 4. Spectral flow phasicity is markedly dampened in the left mid subclavian vein (a) compared to the right (b). (c) Scan of the proximal left subclavian vein shows fresh thrombus as an area of absent flow (arrows) on colour doppler imaging. This patient developed left brachiocephalic/subclavian vein thrombosis after aortic valve replacement surgery.

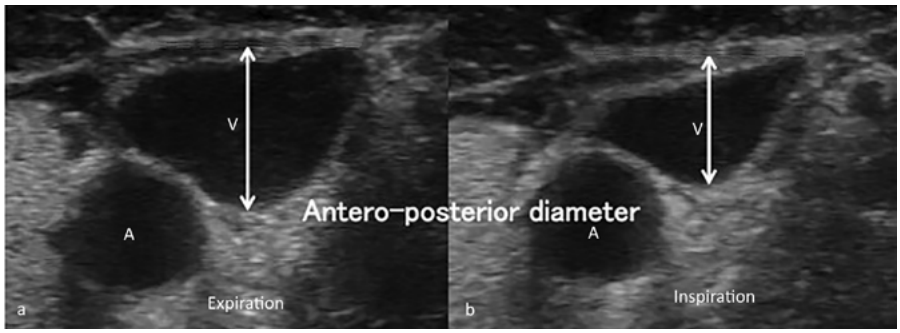


Figure 5. Left subclavian shows normal fluctuation in diameter during expiration (a) and inspiration (b). Absence of such fluctuation in diameter would indicate brachiocephalic vein obstruction either by thrombus or through external compression.

DVT and who have a normal compression ultrasound, it is recommended to repeat compression ultrasound within one week to detect proximal progression of an occult distal thrombus.

While superficial vein thrombosis (e.g. in the greater and lesser saphenous veins) is considered less likely to be a source of emboli, it can extend into the deep veins and ultimately pose the same risk as DVT.

Doppler spectral waveforms are more useful than colour Doppler imaging to assess altered blood flow patterns; changes in these blood flow patterns may indicate venous thrombosis proximal or distal to the examining probe (Fig 3). This is particularly useful when assessing veins that are not accessible to compression (Fig 4).

The subclavian vein shows variation in diameter with respiration (Fig 5) frequently collapsing fully during inspiration. Absence of variation in diameter of the subclavian vein indicates proximal venous occlusion due to thrombus (e.g. with indwelling central venous lines) or extrinsic compression such as may occur with a superior mediastinal mass.

Spectral Doppler evaluation of the common and superficial femoral veins during manual calf compression shows flow augmentation (Fig 6). Absence of this flow augmentation is suggestive of thrombosis in those deep veins located between the examining probe and the compressing hand.

Acute thrombus is often hypoechoic on greyscale US and cannot be distinguished from flowing blood in the vascular lumen (Fig 4c). Organised thrombus is echogenic and usually attached to the vessel wall (Fig 7).

CT and MRI

Thrombus cannot be distinguished from flowing blood within the vessel lumen on non-contrast enhanced CT. Contrast enhancement of the blood pool is required to visualise thrombus; this appears as a hypoattenuating filling defect within the vessel lumen (Fig 8).

CT is particularly useful in deep and central veins, which are not easily accessible to ultrasound compression. It is also useful for identifying the cause (Fig 9) and for distinguishing tumour thrombus from bland thrombus. Bland thrombus

differs from tumour thrombus because the latter shows contrast enhancement while the former does not. Tumour thrombus usually exhibits continuity with the primary tumour and shows enhancement patterns like those of the primary tumour.

On MRI scans, thrombus can be identified without the use of intravenous contrast material; with flow sensitive (bright blood) sequences, thrombus appears as a dark intravascular filling defect within bright flowing blood (Fig 10).

While like CT, contrast-enhanced MRI can distinguish enhancing tumour thrombus from non-enhancing bland thrombus, diffusion weighted imaging (DWI) may be used to avoid contrast material injection. Tumour thrombus shows higher signal and a lower apparent diffusion coefficient (ADC) on DWI than bland thrombus.[7]

Identification of the presence and extent of tumour thrombus is crucial for accurate staging, for treatment planning and for assessing prognosis.[8]

CONCLUSION

In 1865, the French physician Armand Trousseau reported that migratory thrombophlebitis may indicate the presence of occult malignancy. Today, Trousseau's syndrome refers to unexplained thrombotic events, which may precede or occur in parallel with occult visceral malignancy. VTE is seven times more common in patients with known malignancy that in those without. Detection of VTE should therefore prompt a search for underlying malignancy. Conversely, when a malignant lesion is detected on imaging, a search for secondary VTE needs to be considered.

Multimodality imaging allows detection and accurate assessment of extent of VTE. While clinical history may provide a clue to the underlying cause of VTE, multimodality imaging is most useful for detecting co-existing malignant disease, which is often occult at the time of presentation.

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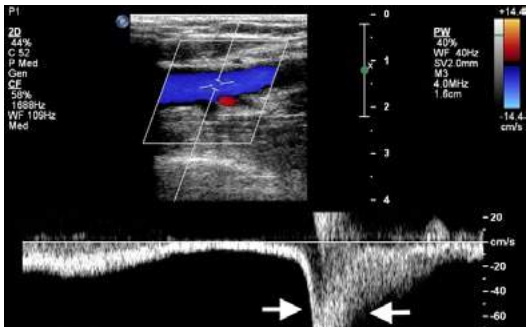

Figure 6. Augmentation of flow through calf compression: spectral doppler image obtained during calf compression (arrows) shows augmentation of flow. This phenomenon helps to exclude thrombosis in deep veins more distal to the examining probe.

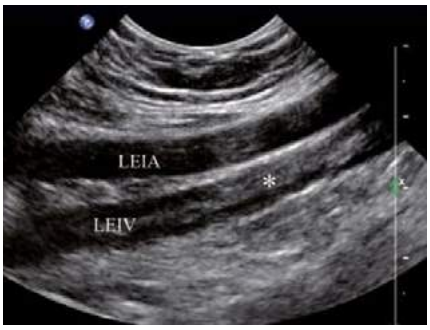

Figure 7. Left external iliac vein (LEIV) contains organised echogenic thrombus (*). (LEIA: left external iliac artery).

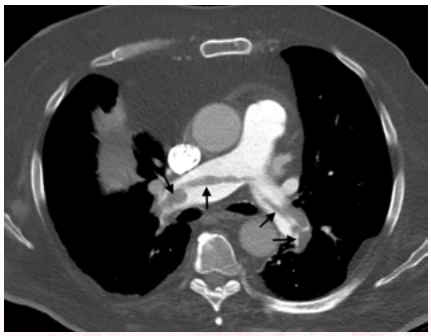

Figure 8. Hypoattenuating filling defects (arrows) in both main pulmonary arteries on contrast enhanced CT represent pulmonary emboli, which are thrombi that have migrated from the deep veins of the lower extremities.

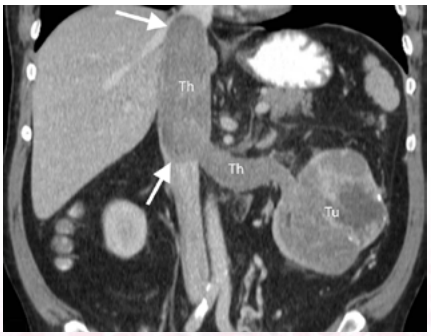

Figure 9. CT showing a left renal cell carcinoma (Tu) with tumour thrombus (Th) extending into the left renal vein and inferior vena cava.

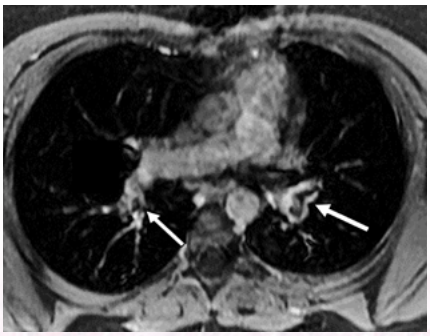

Figure 10. MRI bright blood sequence showing filling defects (arrows) in the main branches of the pulmonary arteries in a patient on oral contraceptives.

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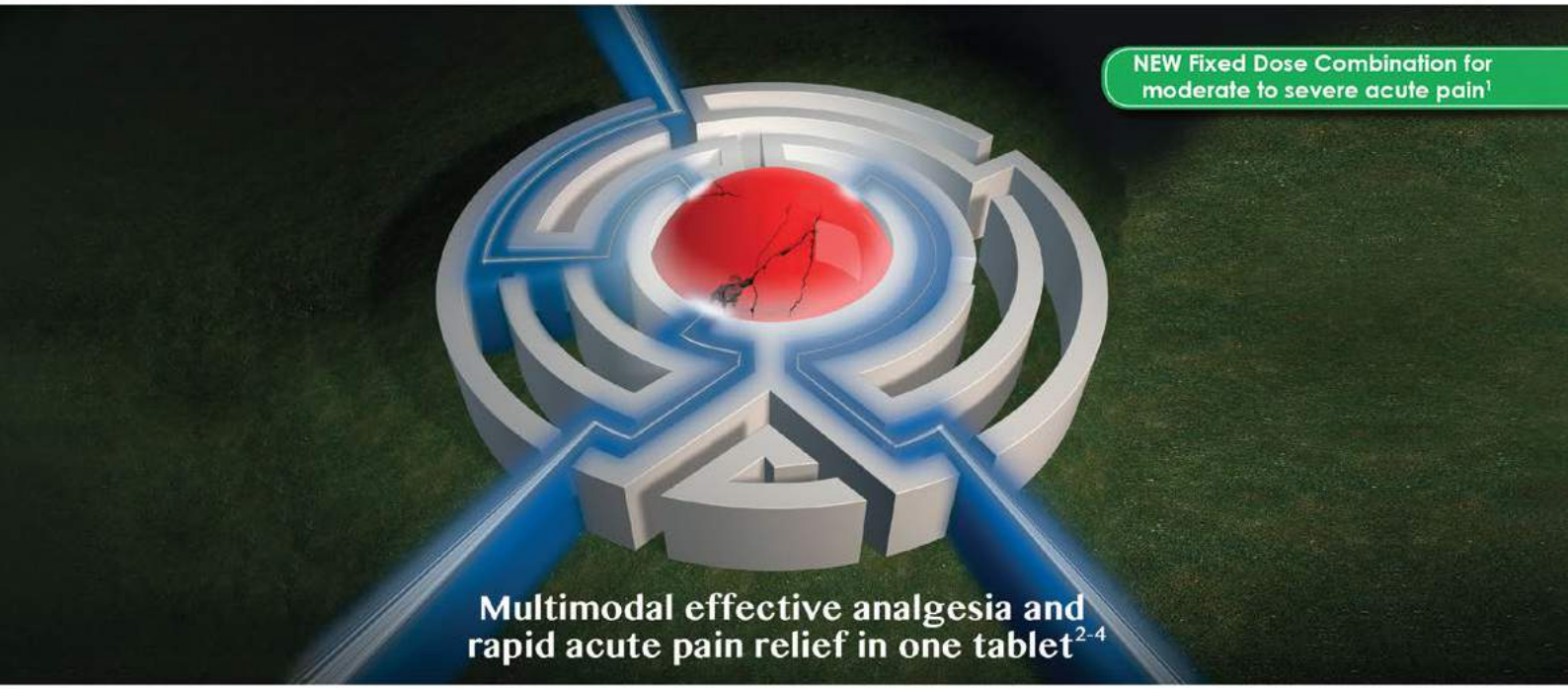

Therapeutic indications

Symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen[4]

Posology

Adults: the recommended dosage is one tablet. Additional doses can be taken as needed, with a minimum dosing interval of 8 hours[4]

PRESCRIBING INFORMATION (For more detailed information, please refer to the full Summary of Product Characteristics)
CLINICAL PARTICULARS Therapeutic indications Symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen. **Posology and method of administration** Posology *Adults*: The recommended dosage is one tablet (corresponding to 75 mg of tramadol hydrochloride and 25 mg of dexketoprofen). Additional doses can be taken as needed, with a minimum dosing interval of 8 hours. The total daily dose should not exceed three tablets per day (corresponding to 225 mg of tramadol hydrochloride and 75 mg of dexketoprofen). Skudexa is intended for short term use only and the treatment must be strictly limited to the symptomatic period and in any case not more than 5 days. Switching to a single agent analgesia should be considered according to pain intensity and response of the patient. Undesirable effects may be minimised by using the lowest number of doses for the shortest duration necessary to control symptoms (see section 4.4). *Elderly*: In elderly patients the starting recommended dosage is one tablet; additional doses can be taken as needed with the minimum dose interval of 8 hours and not exceeding the total daily dose of 2 tablets (corresponding to 150 mg of tramadol hydrochloride and 50 mg of dexketoprofen). The dosage may be increased to a maximum of 3 daily tablets as recommended for the general population only after good general tolerance has been ascertained. Limited data are available in patients over 75 years, therefore SKUDEXA should be used with caution in these patients (see section 4.4). *Hepatic impairment*: Patients with mild to moderate hepatic dysfunction should start therapy at reduced number of doses (total daily dose 2 tablets Skudexa) and be closely monitored. Skudexa should not be used in patients with severe hepatic dysfunction (see section 4.3). *Renal impairment*: The initial total daily dosage should be reduced to 2 tablets Skudexa in patients with mildly impaired renal function (creatinine clearance 60 - 89 ml / min). Skudexa should not be used in patients with moderate to severe renal dysfunction (creatinine clearance ≤59 ml / min) (see section 4.3). *Paediatric population*: The safety and efficacy of Skudexa in children and adolescents have not been established. No data are available. Therefore, Skudexa should not be used in children and adolescents. Method of administration Oral use. Skudexa should be swallowed with a sufficient amount of fluid (e.g. one glass of water).
Concomitant administration with food delays the absorption rate of the drug (see Section 5.2), for a faster effect the tablets may be taken at least 30 minutes before meals. **Contraindications** The contraindications reported for dexketoprofen and tramadol as single agents should be taken into account. Dexketoprofen must not be administered in the following cases: hypersensitivity to dexketoprofen, to any other NSAID, or to any of the excipients listed in section 6.1; patients in whom substances with a similar action (e.g. cetylsalicylic acid, or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticarial or angioneurotic oedema; known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates; patients with active peptic ulcer/gastrointestinal haemorrhage or any history of gastrointestinal bleeding ulceration or perforation; patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy; patients with chronic dyspepsia; patients who have other active bleedings or bleeding disorders; patients with Crohn's disease or ulcerative colitis; patients with a history of bronchial asthma (even if not drug-induced); patients with severe heart failure; patients with moderate to severe renal dysfunction (creatinine clearance <59 ml/min); patients with severely impaired hepatic function (Child-Pugh C); patients with haemorrhagic diathesis and other coagulation disorders; patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake). Tramadol must not be administered in the following cases: hypersensitivity to tramadol or to any of the excipients listed in section 6.1; in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products; in patients receiving MAO inhibitors, or who have taken them within the last 14 days (see section 4.5); in patients with epilepsy not adequately controlled by treatment (see section 4.4); Severe respiratory depression Skudexa is contraindicated during pregnancy and lactation (see section 4.6). **Special warnings and precautions for use** The special warnings and precautions reported for dexketoprofen and tramadol as single agents should be taken into account. (For more detailed information, please refer to the full Summary of Product Characteristics). **Interactions with other medicinal products and other forms of interaction** No clinical studies have been performed to evaluate the potential impact of drug-drug interactions on safety profile of Skudexa. However, those reported for dexketoprofen and Tramadol as single agents should be taken into account. (For more detailed information, please refer to the full Summary of Product Characteristics). **Fertility, pregnancy and lactation** Pregnancy No cases of pregnancy occurred during the Skudexa clinical development. The safety profile of Skudexa during pregnancy has not been established in the clinical studies included in this section. Data reported for dexketoprofen and tramadol as single agents should be taken into account. (For more detailed information, please refer to the full Summary of Product Characteristics). Breastfeeding No controlled trials have been conducted to study the excretion of Skudexa in human milk. Data reported for dexketoprofen and tramadol as single agents should be taken into account. (For more detailed information, please refer to the full Summary of Product Characteristics). Fertility As with other NSAIDs, the use of dexketoprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of dexketoprofen should be considered. **Effects on ability to drive and use machines** The effects known for the single components of Skudexa apply to the fixed combination. (For more detailed information, please refer to the full Summary of Product Characteristics). **Undesirable effects** The adverse events at least possibly related reported in the clinical trials performed with Skudexa and the adverse reactions reported in dexketoprofen and tramadol tablets SmPCs are tabulated below, classified by system organ class. In clinical studies the most commonly observed adverse reactions were vomiting, nausea and dizziness (2.9%, 2.7% and 1.1% of patients, respectively). (For more detailed information, please refer to the full Summary of Product Characteristics. **Overdose** No cases of overdose have been reported in the clinical studies. Data reported for dexketoprofen and tramadol as single agents should be taken into account. (For more detailed information, please refer to the full Summary of Product Characteristics).

[1]*Skudexa, Summary of Product Characteristics* [2]*McQuay HJ et al. Br J Anaesthesia. 2016; 116:269-276*
[3]*Moore RA et al. BMC Anaesthesiol 2016;16:9* [4]*Moore RA et al. The Journal of Headache and Pain. 2015; 16:60*

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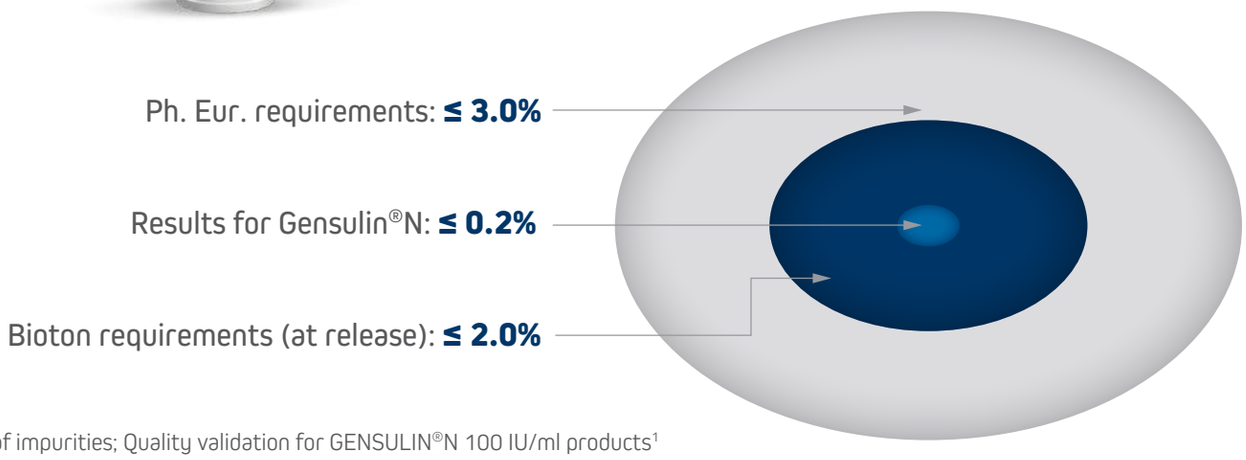
- High product purity[1]
- Long-term stability – **36 months** shelf life[2]
- In-use stability confirmed in studies up to 30°C and 75% of humidity[2]



% of impurities; Quality validation for GENSULIN®N 100 IU/ml products[1]

Long-term stability of GENSULIN®[2]

Examined parameter	Acceptance criteria	Results/Time points in which testing occurred			
		0 month	12 months	24 months	36 months
Human insulin content	95.0-105.0 IU/ml	102.2 IU/ml	102.4 IU/ml	102.9 IU/ml	**101.5 IU/ml**
Content of impurities of molecular weight exceeding insulin molecular weight	≤ 2.0%	0.1%	0.2%	0.3%	**0.5%**
Related proteins: – A21-desamido insulin – Related proteins in total (without A21-desamido insulin)	≤ 2.5% ≤ 3.0%	0.1% 0.9%	0.1% 1.1%	0.1% 1.3%	**0.1%** **1.5%**

Quality validation for GENSULIN®R 100 IU/ml products[2]

High quality manufacturing process

Modern EU-GMP certified biotechnology facility in Poland

Full cycle of insulin production from biosynthesis to packaging (cartridges &vials)

GENSULIN®– Evidence based efficacy and safety[4,5,6,7,8]

PROGENS FIRST STEP

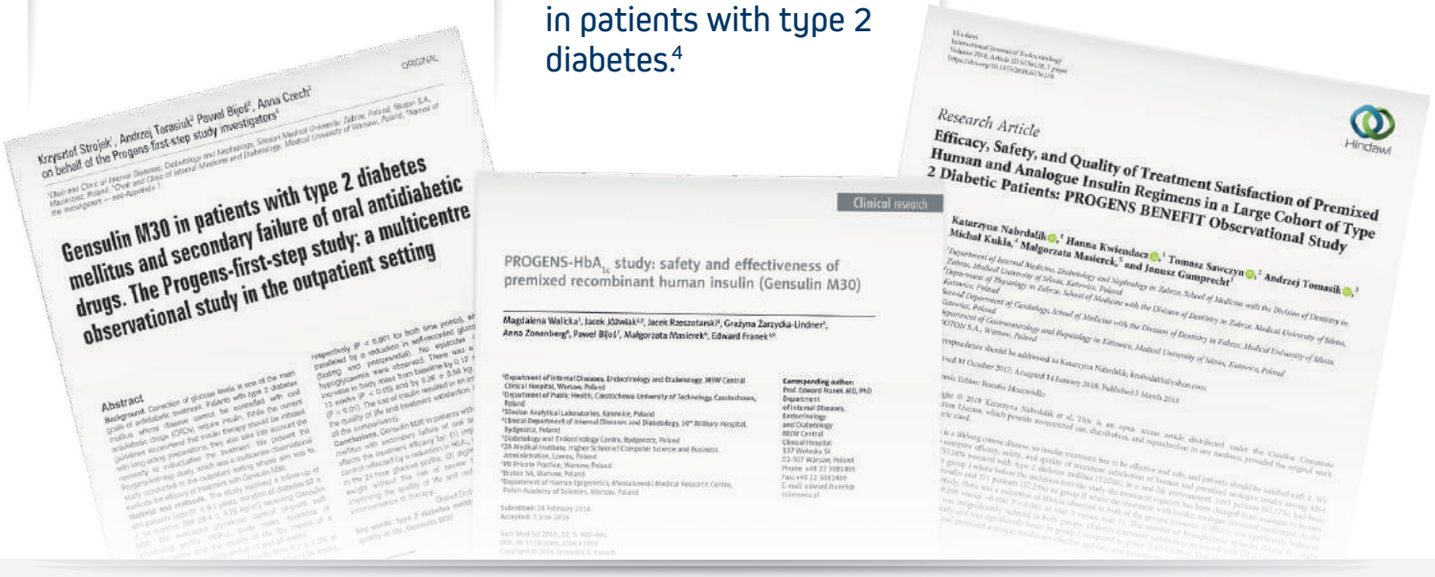
study proved that GENSULIN® M30 in patients with type 2 diabetes and secondary failure of oral antidiabetic drugs **improves glycemic control**, reflected by a reduction of HbA_{1C} and glucose levels.[5]

PROGENS HbA_{1C}

study demonstrated a significant, continuous **decrease of HbA_{1C}** levels, along with **fasting and postprandial plasma glucose**, during treatment with the premixed recombinant human insulin GENSULIN®M30, in patients with type 2 diabetes.[4]

PROGENS BENEFIT

study proved that both human and premixed analogue insulin are **effective and safe** and patients are satisfied with the treatment.[8]



GENSULIN® preparations contain human insulin hormone obtained by E.coli DNA recombination, which similarly to insulin produced in a human body works by lowering levels of glucose (sugar) in the blood. 1 ml of GENSULIN® preparation contains 1001U of human insulin and can be delivered in 10 ml vials or 3 ml cartridges. GENSULIN® R, is a solution for injection of a short-acting insulin that starts to work within 30 minutes after injection, peaks in 1 to 3 hours, and keeps working for up to 8 hours. GENSULIN® N, is an isophane suspension for injection of an intermediate-acting insulin that starts to work within 1.5 hour after injection, peaks in 3 to 10 hours, and keeps working for up to 24 hours. GENSULIN® M30, is a premix of isophane suspension and solution for injection that starts to work within 30 minutes after injection, peaks at 2 to 8 hours and keeps working for up to 24 hours. Therapeutic indications: Diabetes of patients requiring insulin administration in order to maintain proper glucose metabolism. Gestational diabetes. Posology: Dosage is determined by the doctor on the basis of patient's insulin requirement. In type 2 diabetes the average initial dose is 0.2 IU/kg body weight. GENSULIN® R in cartridges is indicated only for subcutaneous injections with a multiple use pen injector. GENSULIN® R in cartridges must not be administered intravenously or intramuscularly. GENSULIN® R in vials can be administered subcutaneously and in special cases intramuscularly and intravenously. GENSULIN® R can be used in intensive insulin therapy as nutritional or prandial insulin. GENSULIN® R should be administered within 15 minutes before a meal. GENSULIN® N in cartridges is indicated only for subcutaneous injections with a multiple use pen injector. GENSULIN® N in cartridges must not be administered intravenously or intramuscularly. GENSULIN® N in vials can be administered subcutaneously and in special cases intramuscularly. GENSULIN® N in vials must not be administered intravenously. GENSULIN® N can be used in intensive insulin therapy to ensure basic insulin secretion. GENSULIN® N can be used at initiation of insulin therapy in type 2 diabetes. The most popular scheme is a once daily injection in the evening time. GENSULIN® M30 in cartridges is indicated only for subcutaneous injections with a multiple use pen injector. GENSULIN® M30 in cartridges must not be administered intravenously or intramuscularly. GENSULIN® M30 in vials can be administered subcutaneously and in special cases intramuscularly. GENSULIN® M30 in vials must not be administered intravenously. GENSULIN® M30 can be used in classical insulin therapy. The most popular scheme is 1, 2 or 3 injections daily. GENSULIN® M30 should be administered within 15 minutes before a meal. Subcutaneous injections should be made in the abdominal area, buttocks, thigh or upper arm. The injection site should be changed to prevent skin thickening. Injections should be made at different sites in the same anatomic area, the same site should not be used more than once a month. While making an injection, caution should be used to prevent needle insertion into a blood vessel. Do not massage the injection site after insulin administration. GENSULIN® products can be used in combination with oral diabetes medications, e.g. metformin or glimepiride. Contraindications: hypoglycaemia, hypersensitivity to insulin or to any of the excipients, unless it is a part of a desensitisation programme. Special warnings and precautions for use: A change of the type or brand of insulin used requires doctor's supervision and may require dose modification. Inappropriate dosing or therapy discontinuation may cause hyperglycaemia and ketoacidosis —life threatening conditions. Human insulin administration can lead to production of antibodies, however their titre is lower than in the case of purified animal insulin. Insulin requirement can change significantly with pancreatic, adrenal, pituitary and thyroid disease, renal or hepatic dysfunction. Insulin requirement can increase during high fever, severe infection, diseases and disorders of the alimentary tract with nausea, vomiting, diarrhoea, delayed gastric emptying and absorption disorders and also during emotional disturbances. Dose modification can be required when the patient changes their physical activity or diet. Patients intending to cross at least two time zones should consult their doctor with respect to the modification of the insulin administration mode. During an air trip, insulin should be kept in the hand luggage and not in a luggage hatch (it must not be frozen). Cardiac insufficiency cases have been reported with concomitant administration of insulin with pioglitazone, especially in patients with cardiac insufficiency risk factors. Undesirable effects: hypoglycaemia, topical allergic reaction, systemic allergic reactions indicative of generalised hypersensitivity to insulin, lipodystrophy at injection site. Following adverse reactions have been reported during post-marketing experience: cases of oedema, cases of weight gain, injection site reactions: discoloration, bleeding, induration, mass, nodule, pain, rash, urticaria, pustule; cases of pruritus and generalized pruritus, cases of dizziness. Marketing Authorisation Holder: BIOTON S.A., Ul. Starokiriska 5, 02-516 Warsaw, Poland. Availability category: The medicinal product is prescribed by a doctor. GensuPen 2 meets the requirements of PN-EN ISO 11608-1 in terms of general requirements, dosing accuracy and resistance to external factors. GensuPen 2 is designed for use with type A needles according to EN ISO 11608-2. The GensuPen 2 should be replaced with a new one aNer about 2 years of use, according to doctor's decision, or in any case of doubts about its proper functioning. The exchange should be made by leading physician (eg Diabetologist) or at a diabetes nurse.

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