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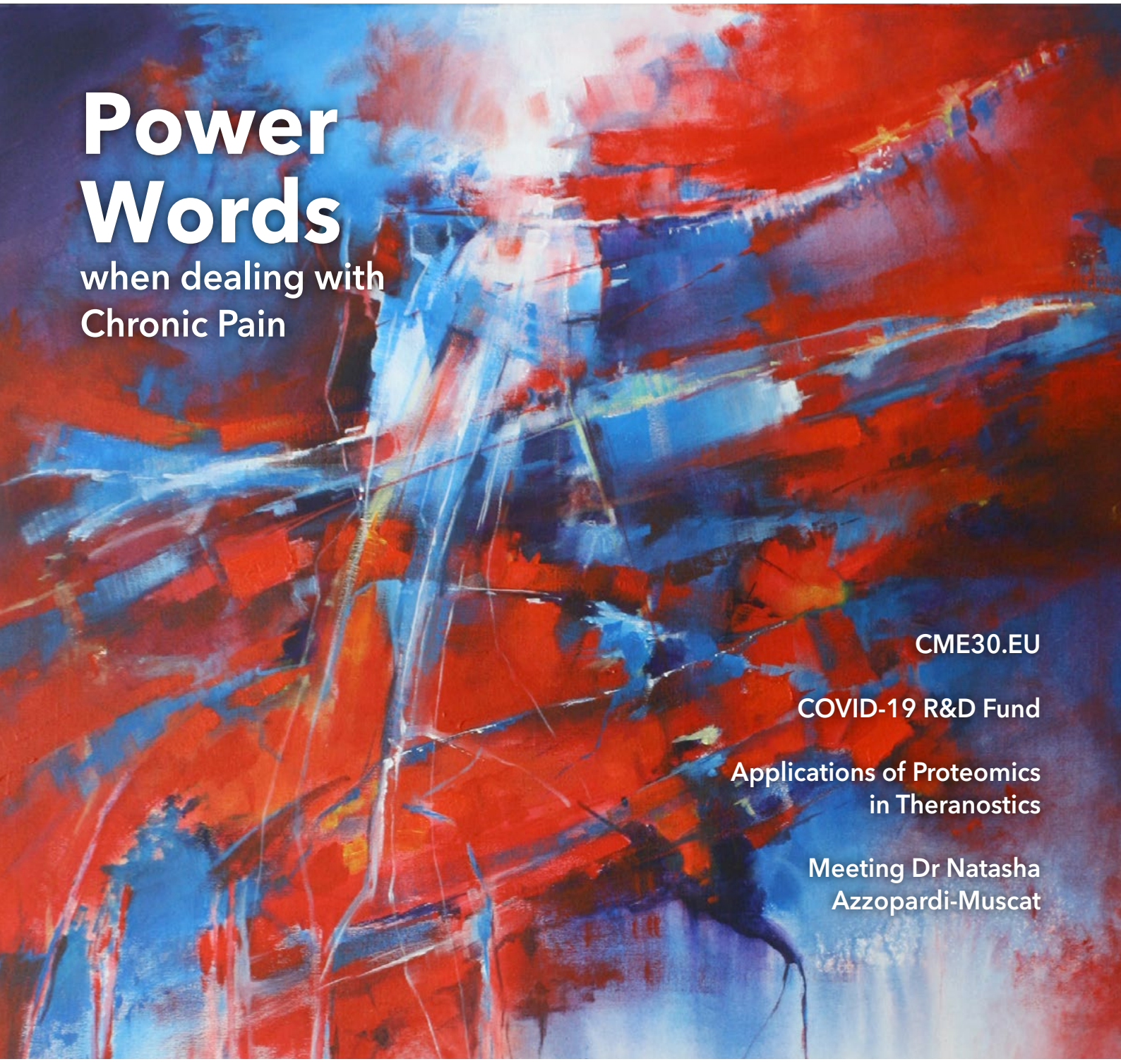
thesynapse

THE MEDICAL PROFESSIONALS' NETWORK



Power Words

when dealing with Chronic Pain

CME30.EU

COVID-19 R&D Fund

Applications of Proteomics in Theranostics

Meeting Dr Natasha Azzopardi-Muscat

Strong glycaemic control[1], in a simple and patient-friendly administering device[2]

Proven CV protection in a wide range of T2DM patients[3]

REWIND®
Trulicity CV Outcomes Trial

trulicity®
dulaglutide once-weekly injection

TRULICITY® PRESCRIBING INFORMATION
(dulaglutide)
Presentation: Dulaglutide solution for injection in a pre-filled pen. Each single-use pen contains either 0.75 mg or 1.5 mg of dulaglutide in 0.5 ml solution. **Uses** Dulaglutide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes. **Dosage and Administration:** Monotherapy: Recommended dose 0.75 mg once weekly. Add-on therapy: Recommended dose 1.5 mg once weekly. For potentially vulnerable patients, 0.75 mg once weekly can be considered as a starting dose. Trulicity is administered as a subcutaneous injection in the abdomen, thigh, or upper arm. It should not be administered intravenously or intramuscularly. The dose can be administered at any time of day, with or without meals. When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When Trulicity is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When it is added to existing sulphonylurea or insulin therapy, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended. Elderly: No dose adjustment is required based on age. Renal impairment: No dose adjustment is required in mild, moderate or severe renal impairment (eGFR < 90 to ≥ 15 mL/min/1.73m). Not recommended in end stage renal disease (< 15 mL/min/1.73 m). Hepatic impairment: No dose adjustment is required. Paediatric: The safety and efficacy of dulaglutide in children < 18 years have not been established. No data are available. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Special Precautions:** Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Dulaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin. Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with dulaglutide, especially at the initiation of treatment. Many of the reported adverse renal events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Patients treated with dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal side-effects and take precautions to avoid fluid depletion.Not recommended in patients with severe gastro-intestinal disease, including severe gastroparesis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. Use of dulaglutide in combination with a sulphonylurea or insulin may increase the risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea or insulin. Trulicity is sodium-free (< 1mmol sodium (23 mg) per 1.5 mg dose). **Interactions:** Dulaglutide delays gastric emptying. For oral medicinal products requiring rapid gastrointestinal absorption, or prolonged release formulations, there is potential for altered drug exposure. Dulaglutide should not otherwise affect the absorption of orally administered medications. Interaction studies with specific medicinal products have been conducted. No dose adjustments of paracetamol, atorvastatin, digoxin, lisinopril, metoprolol, warfarin, oral contraceptives, or metformin (immediate release formula) are required when given together with dulaglutide. For further details of these interaction studies, please see the Summary of Product Characteristics. **Fertility, pregnancy and lactation:** Not recommended during pregnancy. Should not be used if breast-feeding. Effect on fertility is unknown. **Effects on ability to drive and use machines:** When used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable Effects:** Very common (≥ 1/10): Hypoglycaemia (when used in combination with insulin, glimepiride, metformin, or metformin plus glimepiride), nausea, diarrhoea, vomiting, abdominal pain. Common (≥ 1/100 to < 1/10): Hypoglycaemia (when used as monotherapy, in combination with metformin plus pioglitazone, or in combination with an SGLT2 inhibitor with or without metformin), decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastro-oesophageal reflux disease, eructation, fatigue, sinus tachycardia, first-degree atrioventricular block (AVB). Uncommon (≥ 1/1,000 to < 1/100): Hypersensitivity, dehydration, injection site reactions, cholelithiasis, cholecystitis. Rare (≥ 1/10,000 to < 1/1,000): Acute pancreatitis, anaphylactic reaction, angioedema. Not Known (cannot be estimated from available data): Non-mechanical intestinal obstruction. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies. **Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Suspected adverse reactions should be reported to Charles de Giorgio Pharmacovigilance (mobile number: 9974 1387) or cases may be also reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority - Medicines Authority,Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000Malta, E-mail: info.medicinesauthority@gov.mt, Telephone: 356 2343 9000 (from 7:30 to 15:45) Helpline: 356 2343 9111 (from 9:00 to 12:00), Fax: 356 2343 9161). Legal Category:** POM. **Marketing Authorisation Numbers and Holder:** EU/1/14/958/002, EU/1/14/956/007. Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands. Cost (Malta only): 139.90 EUR per pack of 2 single use pre-filled pens. **Date of Preparation or Last Review:** October 2019. Important notice: Information prepared is for healthcare providers only.Trulicity is dispensed upon prescription only.Before prescribing Trulicity, you are kindly asked to read full Summary of Product Characteristics. More detailed information about Trulicity and last revision of text Summary of Product Characteristics are available from Eli Lilly (affiliate name and contact details below) and on the European Medicines Agency (EMA) website: http://www.ema.europa.eu, and/or on European Commission website: http://ec.europa.eu/health/documents/community-register/html/alfregister.htm.

References:
1. Trulicity prescribing information. 2. Trulicity instructions for use. 3. Gerstein et al. Lancet 2019; 394: 121–130.

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Charles de Giorgio Ltd.

Lilly

Authors

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health for these last 30 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-authors of the article are Dr Michael Balzan.

Dr Muriel Bellizzi MD MSc(Clin Pharm) DESA DEPM(ESRA) is a specialist registrar with the Department of Anaesthesia, Intensive Care and Pain Medicine. She trained in Acute and Chronic Pain at the Oxford University Hospitals in the UK and is currently part of the pain clinic team at Mater Dei Hospital.

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

Cover:
A recent work by John Martin Borg in acrylic. In this work the artist is exploring the limited use of his palette, reducing it to two basic colours, red and blue. At the same time he is creating a dramatic composition by fragmenting one of his colours, undoubtedly this must have been influenced by the period the work was created, that of the 'Covid 19 lockdown', that seems to have shuttered our tranquility. The end result is a vibrant and provocative abstract.

Issue Guide

TheSynapse

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

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

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OUR COLLABORATORS

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

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Actifed*

Actifed* oral solutions provide symptomatic relief of upper respiratory tract disorders [1-6]

Actifed* DM COUGH LINCTUS

- relieves dry cough and nasal congestion [2,5]

Actifed* SYRUP

- clears blocked and runny noses [1,4]

Actifed* EXPECTORANT

- clears chesty cough and nasal congestion [3,6]

Dosage	
children aged 2 to 5 years [1-3]	2.5ml every 4-6hrs as required
children aged 6 to 11 years [1-3]	5ml every 4-6hrs as required
adults (including the elderly) and children aged 12 years and over [4-6]	10ml every 4-6hrs as required

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

ACTIFED ABRIDGED PRESCRIBING INFORMATION: Please refer to full Summary of Product Characteristics **(SPC)** before prescribing. **TRADE NAME: ACTIFED. ACTIVE INGREDIENT:** Actifed **DM** Cough Linctus**:** Each 5ml contains **D**extromethorphan Hydrobromide 10mg, **P**seudoephedrine Hydrochloride 30mg and **T**riprolidine Hydrochloride 1.25mg; **A**ctifed **S**yrup**:** Each 5ml contains **P**seudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; **A**ctifed **E**xpectorant**:** Each 5ml contains **T**riprolidine Hydrochloride 1.25mg, **P**seudoephedrine Hydrochloride 30mg and **G**uaiphenesin 100mg. **PHARMACEUTICAL FORM: O**ral **S**olution **INDICATIONS: S**ymptomatic relief of upper respiratory tract disorders which are benefited by a combination of**:** Actifed **DM** Linctus**:** a nasal decongestant, an anti-histamine and an antitussive; **A**ctifed **S**yrup**:** a nasal decongestant, and an anti-histamine; **A**ctifed **E**xpectorant**:** a nasal decongestant, an anti-histamine and an expectorant. **DOSAGE:** please refer to full **SPC**. Actifed **DM** Cough Linctus, Actifed Syrup and Actifed Expectorant are authorised for use without the need of a medical prescription in **A**dults and **C**hildren over 12 years. **I**n **C**hildren between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. **CONTRAINDICATIONS: P**revious intolerance to any of the active substances; use of **MAOI**'s in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure. **PRECAUTIONS: M**ay cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment. **INTERACTIONS: S**ympathomimetics; **MAOI**'s. **ADVERSE EVENTS: C**entral nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. **PREGNANCY AND LACTATION: A**dministration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child. **PRESENTATION: DM**Cough Linctus, Expectorant, **S**yrup**: A**mber glass bottle x 100ml.**M**arketing **A**uthorisation Holder**: G**laxo**S**mith**K**line**(I**reland**)** Ltd. **M**arketing **A**uthorisation **N**umber**: MA** 192/02001-6. **L**egal category**: POM – A**ctifed **DM** Cough Linctus, **A**ctifed **S**yrup, **A**ctifed **E**xpectorant in **A**dults and **C**hildren over 12 years. **D**ate of preparation**: O**ctober 2019.

For the latest product information, please refer to the full **SPC** or contact us at **GSK M**alta **(**phone**: +35621238131).**

Suspected adverse events should be reported to **GSK M**alta through**:** gskpro.com/en-mt **(P**hone**: +35621238131, A**ddress**: GSK M**alta, 1 **(**1st floor**),** de la **C**ruz **A**venue, Qormi, **M**alta**). C**ases may also be reported through medicinesauthority.gov.mt/adrportal **(M**alta **M**edicines **A**uthority**)**

References: 1. Actifed Syrup SPC (Nov 2018); 2. Actifed DM Cough Linctus SPC (Nov 2018); 3. Actifed Expectorant SPC (Mar 2019); 4. Actifed Syrup SPC OTC (Nov 2018); 5. Actifed DM Cough Linctus SPC OTC (Nov 2018); 6. Actifed Expectorant SPC OTC (Mar 2019)

PM-MT-NA-ADVR-190001 **P**repared**:** October 2019

"I am justly killed with mine own treachery"

In the last editorial I referred to immunity passports and excess mortality measurements. I will discuss them briefly in relation to SARS-CoV-2.

IMMUNITY PASSPORTS

Three words … A terrible notion; but it seems that history truly tries to repeat itself. Back in the 19th century, immunity to yellow fever created a divide in New Orleans [US] between the 'acclimated' who had survived yellow fever and the 'unacclimated', who did not contract the disease. Any lack of immunity dictated where people could work, whom they could marry, and, for slaves, their worth.[1] The idea of immunity passports recently floated by various countries including the US, UK and Germany is that governments issue them to those who have recovered and tested positive for antibodies to SARS-CoV-2. This means that authorities would lift restrictions on those passports carriers, allowing them to socialize, travel and obviously return to work. Nonetheless, practical challenges as well as ethical ones make this concept a very bad idea since this attacks the very principle of social justice … problems relate to issues stemming from unreliability of specific serological tests, still unanswered questions on SARS-CoV-2 immunity, unfair access to testing, public health threats [non-immune individuals may wilfully seek out infection to access any social and economic liberties given only to people who have recovered from COVID-19] and also, the fact that the volume of testing needed is unfeasible.

EXCESS MORTALITY MEASUREMENTS

Excess mortality measurements can prove to be a superior tool to officially confirmed Covid-19 deaths since they measure the additional deaths in a given time period compared to the number usually expected, and does not depend on how Covid-19 deaths are recorded. This has been advocated by various public health specialists and medical statisticians worldwide to mitigate intentional or unintentional under-reporting of Covid-related deaths especially in the elderly population residing in nursing homes. Obviously this measuring tool is mostly applicable to large countries and/or countries who have a failing healthcare system. In fact when official Covid-related deaths of specific cities and countries are compared with excess mortality measurements, gaps have been identified, at times abyssal ones. Let me give some examples. Between April and July 2020 Peru had 19,000 official Covid-related deaths, yet it had 55,000 excess deaths. And between March and July 2020 Spain had 28,000 official Covid-related deaths, yet it had 43,000 excess deaths. Many other European countries experienced such periods of excess mortality. One should also factor the indirect impact of the pandemic, such as non-Covid deaths related to delayed access to healthcare. In keeping with this, the pandemic has also accentuated the widening health divide of populations with the more deprived populations and ethnic minority communities suffering the brunt.

The balancing act between health and economics is a tricky business. Quite possibly, if policy makers were to look at the doughnut model of economics developed by the Oxford economist Kate Raworth, one could come up with measures to help mitigate some of the challenges which are inherent in this relationship. In Act 5, Scene 2 of Shakespeare's Hamlet, Laertes says to Osric *"I am justly killed with mine own treachery."* My augur is that we do not end up quoting Laertes when we will be discussing our actions in relation to SARS-CoV-2 with future generations … we were justly killed with our own treacheries …

REFERENCE

1. Olivarius K. *Am. Hist. Rev.* 2019; 124(2):425–455.

SEROXAT

The Anxiolytic Antidepressant:[1,2]

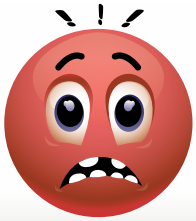
Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]



Panic Disorder[3]

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

SEROXAT ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: SEROXAT. ACTIVE INGREDIENT: Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20mg. **INDICATIONS:** Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with and without agoraphobia, Social Anxiety Disorders/Social phobia, Generalised Anxiety Disorder, Post-traumatic Stress Disorder. POSOLOGY: Administer once daily in the morning with food. Refer to full SPC for dosing information for specific conditions. Withdrawal symptoms seen on discontinuation of Paroxetine: abrupt discontinuation should be avoided. ***Elderly:*** maximum dose should not exceed 40mg daily. ***Children and adolescents:*** Should not be used. ***Renal/hepatic impairment:*** Dose should be restricted to lower end of dosage range. **CONTRAINDICATIONS:** Hypersensitivity. Should not be used in combination with MAOIs, thioridazine or pimozide. **PRECAUTIONS:** Treatment should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAOI; Do not use in children and adolescents under the age of 18 years; Suicidal thoughts or clinical worsening: an improvement may not occur in the first few weeks of treatment: patients should be closely monitored; Use of paroxetine has been associated with development of akathisia: most likely to occur within first few weeks of treatment: do not increase dose in these patients; Serotonin syndrome/ neuroleptic malignant syndrome may develop rarely: treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. Do not use in combination with serotonin-precursors; Use with caution in patients with a history of mania, severe renal and hepatic impairment, diabetes (there have been studies suggesting an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered) and in epilepsy; Drug should be discontinued if patients who develop seizures; There is little clinical experience of concurrent use with ECT; Use with caution in narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia; Caution when administered concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase risk of bleeding; Paroxetine may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen: concomitant use should be avoided; Withdrawal symptoms may occur on discontinuation of Paroxetine treatment. *Refer to full SPC for information on drug interactions*. **PREGNANCY/FERTILITY/LACTATION:** ***Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated due to potential increased risk of cardiovascular malformations during the first trimester; symptoms such as respiratory distress, cyanosis, apnoea, seizures and other complications may occur in the neonate after maternal paroxetine use in later stages of pregnancy and increased risk of persistent pulmonary hypertension of the newborn (PPHN). ***Lactation:*** Use during lactation can be considered. **UNDESIRABLE EFFECTS:** ***Very Common (≥ 1/10):*** Nausea, Sexual dysfunction; ***Common (≥ 1/100, <1/10):*** Increases in cholesterol levels, decreased appetite, somnolence, insomnia, agitation, abnormal dreams (including nightmares), dizziness, tremor, headache, impaired concentration, blurred vision, yawning, constipation, diarrhoea, vomiting, dry mouth, sweating, asthenia, body weight gain; Increased risk of bone fractures in patients receiving SSRIs and TCAs; Common withdrawal symptoms include: dizziness, sensory disturbances, sleep disturbances, anxiety, headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility were observed. ***Refer to full SPC for the full list of adverse reactions.*** **LOCAL PRESENTATIONS:** 20mg Tablets (by 30 tablets). MARKETING AUTHORISATION HOLDER: GlaxoSmithKline (Ireland) Ltd **MARKETING AUTHORISATION NUMBERS:** MA192/02501. **LEGAL CATEGORY:** POM. DATE OF PREPARATION: May 2019.

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

REPORTING ADVERSE EVENTS (AEs):

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

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

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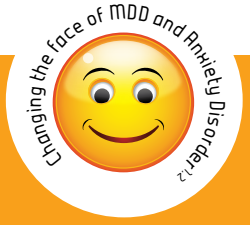

Reference: 1. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH *et al.* Practice guideline for the treatment of patients with major depressive disorder (Third Edition) American Psychiatric Association 2010. 2. Baldwin et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology Journal of Psychopharmacology 1–37 2014. 3. Seroxat SPC March 2019.

Job No: PM-MT-PRX-ADVR-190001 Date of preparation: August 2019

COVID-19 R&D Fund

At the beginning of April 2020, over 1 million active COVID-19 cases with over 59,000 deaths were reported. By early June 2020, cases soared to over 7 million with over 400,000 deaths affecting over 200 countries. Different trends were observed in different regions, with the situation stabilising in some, while still peaking in others. Due to the observed socio-economic impact, the European Commission (EC) adopted the Temporary Framework for State Aid Measures to Support the Economy in the Current COVID-19 Outbreak which enables Member States to administer State Aid funds. Through this framework the Maltese Ministry for Finance and Financial Services and the Ministry for the Economy, Investment and Small Businesses, took the opportunity to launch a national COVID-19 Research and Development (R&D) Fund.

The Malta Council for Science and Technology (MCST) and Malta Enterprise (ME) came together to administer the COVID-19 R&D Fund. Both governmental entities are well-known key enablers that manage national funds that help support research, innovation and development undertaken by public, private and academic entities. The COVID-19 R&D fund will see **€5.3M** funnelled into developing innovative and improved scientific and technological approaches to the challenges raised by COVID-19 and future pandemics. Interested project ideas must have a clear COVID-19 link and encompass an inherent research uncertainty that is explored through one of the three parameters that define R&D i.e.:

- **Fundamental research:** experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any direct commercial application or use in view;
- **Industrial research:** investigative work aimed at developing new or improving on existing products, processes, and services;
- **Experimental development:** the acquisition and combination on existing scientific knowledge with the aim of prototyping, demonstrating, piloting and validating new or improved products.

Interested applicants must have an operating base in Malta and may apply under one of two routes:

1. State Aid support under the Temporary Framework for applicants that are undertakings and/or where the project proposal is deemed to be of an economic nature;
2. Non-State Aid route which applies to public entities and where the project proposal is deemed to be non-economic in nature.

The aid intensity varies, depending on the route taken. If approved, Non-State Aid applications may receive funding with an aid intensity of up to 100%, while State Aid applications may receive funding with an aid intensity between 80% to 100% depending on the applicable R&D definition chosen. The COVID-19 R&D Fund has no grant size capping, hence interested applicants may apply for as large a sum as necessary to fulfil their project needs.

This is an open call which will run till the 30th of November 2020. Eligible projects must have started not earlier than the 1st of February and not later than the 31st of December 2020. There is no minimum duration, however the maximum duration of the project is 18 months. Interested applicants may find more details related to the Rules for Participation and Application form here: https://mcst.gov.mt/ri-programmes/covid-19-rd-fund/ or https://covid19.maltaenterprise.com/covid-19-rd-fund/. Any specific queries related to the aforementioned documents and Fund can be forwarded to **ri.mcst@gov.mt**.

DR ALFRED GRECH AND DR MICHAEL BALZAN

Brief Overview of The Applications of Proteomics in Theranostics

ABSTRACT

Theranostics is an emerging field of medicine that uniquely combines drugs and/or techniques to simultaneously or sequentially diagnose and treat medical conditions. Proteomics, the large-scale characterisation of proteins, is now being applied in theranostics. The proteome is the entire set of proteins that is produced by an organism. It varies temporally and spatially according to the distinct needs of the organism. Major breakthroughs in human proteomics are seen in its theranostics applications as biomarkers (e.g. in cancer, Alzheimer's disease, various other neurodegenerative disorders, autism, cardiovascular diseases) and in therapeutics (e.g. personalised treatment).

INTRODUCTION

Proteomics is the analytical study of all proteins transcribed by a genome.[1] It was Anderson and Anderson in 1977 who pioneered in this field by studying human plasma proteins. They even predicted that someday all proteins in the human body could be identified.[2]

Human proteomics is catalysing a new research field that has the potential to be translated into the clinical setting. This 'clinical proteomics' is trying to understand what, how much and when, certain proteins are expressed in health and disease. Thus, it has the potential to help in the discovery of novel biomarkers of disease processes and help to improve their diagnosis and prognosis.[3-5] Also proteomic profiles have great potential to unveil pathophysiological circuits associated with pathology of disease and these may provide targets for new treatments or prevention. They can also offer novel ways for personalised therapeutics.

Amongst the main crucial technologies that are used to identify, quantify and characterise the proteins (and hence describe the proteomic signatures or profiles) of normal and disease processes, a combination of mass spectrometry,[6] two-dimensional electrophoresis[7] and bioinformatics is applied. These powerful technologies, especially quantitative MS and bioinformatics, have made great advances and today it is possible to analyse complex mixtures of proteins in a more rapid, accurate and quantitative way. The field of bioinformatics has advanced to meet the need for data acquisition, interpretation and presentation. These great advances are helping to discover the function of proteins and the underlying pathological mechanisms of disease.

1. PROTEOMICS IN CARDIOVASCULAR DISEASES

Arrell et al.[8] found that in patients with dilated cardiomyopathy (DCM) there are 88 myocardial proteins which have decreased expression. They proposed that this low myocardial protein profile can be used as a diagnostic and prognostic signature for DCM.

Borozdenkova et al.[9] studied proteomic signatures as potential markers for rejection after heart transplants. Of the 100 proteins that they found to be overexpressed, 13 were specific to heart tissue. Of these 13, two proteins, tropomyosin and alpha beta-crystallin, were measurable in the serum of patients having rejection after 3 months.

As mentioned, proteomic bio-profiles can reveal pathophysiological circuits associated with pathology (causation and progression) and these can provide targets for new treatments or prevention. In keeping with this Ferreira et al.[10] initially identified 252 proteins in the plasma of heart failure patients. After factoring a number of variables, the number of circulating plasma proteins associated with heart failure pathophysiology was decreased to 38. These were specifically linked by the authors to apoptosis, inflammation, vascular physiology, remodelling of matrix, control of blood pressure, and cholesterol metabolism [ClinicalTrials.gov Identifier: NCT02556450].

Further to this, Lind et al.[11] have worked on a proteomic chip to discover new biomarkers for AF. Using this chip they discovered that four other proteins, specifically FABP4, IL-6, TIM-1 and AM, besides the already known ones (i.e. NT-pro-BNP, FGF-23, GDF-15) are linked to the development of AF.

2. PROTEOMICS IN MENTAL ILLNESS

The underlying pathophysiology of mental illness remains unclear. Proteomics is one tool that has the potential to objectively help this situation and thus aid in their theranostics.

Xu HB et al.[12] analysed the plasma proteomes of patients with major depressive disorders and healthy controls. They showed expression of altered proteins (A2M and isoform-1 of VDP) involved in immunoregulation and lipid metabolism. They proposed that disruption in immunoregulation and lipid metabolism might be implicated in the pathological mechanisms of major depressive disorders.

In a similar but more recent proteomic study, Smirnova et al.[13] also showed differences in the serum proteomes of schizophrenia and bipolar disorder.[14] Specifically, they discovered 27 proteins for schizophrenia, and 18 proteins for BD. In schizophrenia, the proteins were linked to the immune response, cell growth and maintenance, cell communication, and to the regulation of metabolism of proteins and of nucleic acids. In BD, the proteins were linked to the immune response, cell membrane transportation, communication of cells and their growth, and to neurons and oligodendrocyte development.

As with other proteomic studies in other areas such results will eventually surely unveil the intricate pathways of psychotic disorders with beneficial outcomes in management within the clinical setting.

3. PROTEOMICS IN AUTO-IMMUNE DISEASES

Proteomics is also being applied in auto-immune disease. Wu et al.[15] discovered potential biomarkers for systemic lupus erythematosus (SLE). In this study, SLE serum autoantibodies were validated using serum samples from 306 participants. Four peptides (SLE2018Val001, SLE2018Val002, SLE2018Val006, and SLE2018Val008) were identified as being able to differentiate SLE patients from healthy controls. Wu et al. propose that their approach could be implemented to identify autoantibodies in other diseases.

Xu et al.[16] investigated 106 proteins in patients with psoriasis which are involved in several biological signalling pathways relevant in the disease. Following a comparison with a healthy cohort, the authors found that, of these 106 proteins,58 are only found in psoriatic patients. From these 58, 21 proteins have been identified as markers for treatment outcomes. Furthermore, 3 proteins showed a reliable correlation with the severity of the disease.

In rheumatoid arthritis, serum amyloid A (SAA) and S100 have already been identified as potential biomarkers. Nys et al.[17] furthered the research and found that there is a negative relationship between the subtypes of SAA, SAA1α and SAA1β for early-onset RA. They also found that isoform SAA2 and S100A8/S100A9 proteins are overexpressed irrespective of the RA phase. They propose that these findings might be indicators of other unknown pathways of the disease.

Another proteomic study in RA patients was done by Chen et al.[18] They analyzed biomarkers to distinguish responders to triple therapy (methotrexate, leflunomide and infliximab). They analysed 51 proteins that were expressed differently in responders and non-responders. Such proteins in proteomics are called differentially expressed proteins (DEPs). Of these DEPs 5 were significantly up-regulated whilst another 5 were down-regulated. This study shows how proteomics can be used as a tool to predict clinical response.

4. PROTEOMICS IN MULTIPLE SCLEROSIS

Malekzadeh et al.[19] studied DEPs during the progression of MS. The study was spread over 4 years and involved a cohort of healthy individuals and 3 cohorts of MS patients with 3 different rates of progression. Importantly they found 8 potential biomarkers, including LGLAS8, CCL3, RGMA, C3, FGF9, and EHMT2. These proteins are associated with complement pathways, activation of the immune system, and cell-cell and cell-matrix adhesions. The authors of the study propose that these proteins are involved in the progression of MS and they envisage further research to use them in the clinical setting.

5. PROTEOMICS IN INFLAMMATORY BOWEL DISEASE (IBD)

Ning L et al.[20] compared proteomic profiles of intestinal tissue taken from healthy individuals, and patients with IBD, specifically Crohn's disease (CD) and ulcerative colitis. They found several DEPs, like angiotensin converting enzyme 2 (ACE2) and angiotensin converting enzyme 1 (ACE), being overexpressed. Such overexpression was more marked in CD. Most importantly they found overexpression of CD38 in inflamed tissue. This is a protein which is intricate in the nicotinamide adenine dinucleotide (NAD)[10] metabolism. They proposed that this finding might need to be followed further to study the function of CD38 and NAD metabolism in intestinal inflammation.

On the other hand Lehmannet al.[21] compared fecal samples taken from patients with CD and UC via a metaproteomic approach. Importantly they found that CD and UC patients showed underexpression of human IgA and the protein RprY from Bacillus fragilis. However, in CD they found an overexpression of the enzyme sucrose-isomaltase. The authors concluded that that, following validation, their fecal metaproteomic approach could be used as a non-invasive way in the diagnosis of CD and UC.

6. PROTEOMICS IN AUTISM

Various causes have been implied in the pathophysiology of autism, but the exact mechanisms remain elusive. Proteomic studies might prove to be useful to uncover these. Junaid et al.[22] used a proteomic profiling method on autopsied brains of Autism Spectrum Disorder patients. They discovered an abnormal protein pattern as a result of an aberrant gene expression in their grey matter. Specifically, they found reduced glyoxalase 1 expression and propose that this gene might be a possible aetiological factor.

In another proteomic analytical study to unveil the underlying mechanisms in autism, Corbett et al.[23] compared protein profiles from two groups of children, one group comprising autistic children and the other comprising a cohort of normal children as control. The study showed that in the autistic group, there was an increased expression of Apolipoprotein B-100,

Complement Factor H Related Protein (FHR1), Complement C1q and Fibronectin 1 (FN1). The authors proposed that these differences might be aetiological factors in the abnormal brain development in autistic children.

7. PROTEOMICS IN CANCER

Proteomic studies are also being integrated with other studies like genomics and transcriptomics. This augments the discovery of the molecular players involved in the pathophysiology of diseases, including cancer. A case in point is the study carried out by Wu et al.[24] Here, analysis of proteomic and transcriptomic profiles showed that the long non-coding RNA molecule HOTAIR (HOX Transcript Antisense Intergenic RNA), which has been implicated in human tumorigenesis, also shows dysregulation in hepatocellular carcinoma (HCC). Specifically, HOTAIR inhibition was found to be associated with dysregulation of several transcripts and proteins. Functional bioinformatic studies of the data collected showed that these transcripts and proteins relate to biological circuits in cancer. Furthermore, the study showed that HOTAIR caused cell proliferation partly by its regulation of OGFr expression (opioid growth factor receptor), the latter being known to have a negative regulation on cell proliferation in HCC.

HOTAIR is also dysregulated (specifically it is overexpressed) in breast cancer. This over-expression is responsible in metastasis through HOTAIR recruitment of another complex molecule called Polycomb repressive complex 2 (PRC2), which then silences additional genes, besides the HOXD gene cluster. In 2016 Meredith et al.[25] carried out a proteomic analysis and found that other proteins are associated with HOTAIR's action. One such significant interaction is that between HOTAIR and hnRNP (heterogeneous nuclear ribonucleoprotein) A2/B1. This interaction is central to chromatin structure regulation in cells of breast cancer. Indeed, the authors found that knocking down A2/B1 reduced PRC2 activity and also cell invasion.

8. PROTEOMICS IN OBSTETRICS AND GYNAE DISORDERS

Tarca et al.[26] carried out a study comparing plasma proteins bio-profiles in 90 normal pregnant women and 33 who had early pre-eclampsia. They discovered that a specific proteomic signature preceded pre-eclampsia. Specifically, at 16-22 weeks matrix metalloproteinase-7 and glycoprotein IIb/IIIa complex were overexpressed and could be used as reliable predictors. Predictors from 22–28 weeks were increased levels of sialic acid binding immunoglobulin-like lectin 6 (siglec-6) and activin-A, and decreased levels of isoform 121 (VEGF-121), placental growth factor (PlGF) and vascular endothelial growth factor A. From 28 weeks to 32 weeks, the best biomarkers were activated leukocyte cell adhesion molecule, siglec-6, and VEGF-121.

In 2019 Eckert et al.[27] used proteomics to characterise pivotal molecules in ovarian cancer, studying the latter phenotype in-situ and its progression in metastasis. They discovered that methyltransferase nicotinamide N-methyltransferase (NNMT) and the proteins that it regulates underpins metastasis. Specifically, they revealed that over-expression of NNMT leads to ovarian cancer cells to migrate and proliferate, causing also a reduction of histone methylation and S-adenosyl methionine. These epigenetic changes caused a global change in gene expression associated with the ovarian cancer phenotype behaviour.

9. PROTEOMICS IN NEURODEGENERATIVE DISORDERS

Mining large data from proteomics, Deolankar et al.[28] propose a new pathway to diagnosis and treat Alzheimer's disease. Specifically, they used spectral data to sieve for protein post-translational modifications, and indeed, found proteins modified post-translationally. They propose that these may be used as biomarkers for diagnosis or as molecular targets for treatment in AD. Of the many novel proteins found, 13 of them showed high expression.

Mallah et al.[29] employed a micro-proteomic platform to find spatiotemporal signatures of protein markers after traumatic brain injuries (TBI) in a rat model. Specifically, they analysed different brain regions at 1 day, 3 days, 7 days, and 10 days, post-injury. They found that there was an over-expression of proteins that are similarly expressed in Parkinson's disease. Amongst these were GPR158, HGMB1, Synaptotagmin and Glutamate Decarboxylase in ipsilateral substantia nigra. The authors propose that their study shows a possible link for PD or Parkinsonism post-TBI.

Amyotrophic lateral sclerosis[14] and frontotemporal dementia (FTD) are two neurodegenerative disorders whose pathophysiology is yet not clear even though the culprits may be the aggregation of abnormal proteins in neurons which lead to their degeneration. The proteins that have been implicated are tau, superoxide dismutase 1 (SOD1) and TAR DNA binding protein of 43 kDa (TDP-43). In this regard, Hedl et al.[30] discuss new technologies and approaches like SILAC (stable isotope labelling by amino acids in cell culture), IP-MS (immunoprecipitation mass spectrometry) and BioID (biotin identification), the latter two being PPI (protein-protein interaction) techniques. These proteomic approaches are high-throughput, quantitative and unbiased. Moreover, they are novel avenues that can be used to unveil the mechanisms of pathology, biomarkers and therapeutic targets for ALS and FTD.

10. PROTEOMICS IN OBESITY

It is a well-known fact that, following bariatric surgery, those obese diabetic patients showing insulin resistance, have their glucose levels controlled, notably after the biliopancreatic diversion, BPD. ClinicalTrials.gov Identifier:

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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. 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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. 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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

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NCT01151917 (2009) conducted between 2009 and 2012employed a proteomic platform to investigate the proteins and peptides that underlie the mechanisms involved in the glycaemic restoration after BPD.

Indeed, Nicolai et al.[31] used mass spectrometry and identified a low-abundance peptide that regulates glucose and appetite. Specifically, they discovered that the secretion of oxyntomodulin, a gut hormone, is increased 10-fold after the gastric bypass in type 2 diabetic patients. They also found that oxyntomodulin is co-secreted with glucagon-like peptide-1 (GLP-1), another gut hormone. Moreover, oxyntomodulin acts using the same receptor as GLP-1 and is deactivated by the same protease that breaks down the latter. Thus, they proposed that oxyntomodulin and GLP-1 may regulate glucose metabolism and appetite.

Such discoveries of low-abundance regulatory peptides show again that the proteomic approach has great potential in therapeutic translational research, namely that of providing new ways to treat insulin resistance.

11. PROTEOMICS FOR THE DISCOVERY OF NOVEL DRUG TARGETS

Proteomics is fast becoming a requisite of the discovery of drugs. This is made possible by the fact that proteomic technologies like MS but also mapping of protein-protein interaction have matured into reliable methods. Indeed, hot spots on suspected culprit proteins are being discovered and offer potential targets for novel therapeutic drugs.

CONCLUSION

In the future, the introduction of new biomarkers into medical practice can influence patients' health in many ways. However, more input is needed before research is turned into a diagnostic test that saves lives.

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Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional using the commercial Taltz 80 mg/1 ml prefilled syringe. For instructions on preparation of Taltz 40 mg, see SmPC. Doses less than 80 mg must be prepared by a healthcare professional. For children prescribed 80 mg, Taltz can be used directly from the prefilled syringe. Use the Taltz 80 mg pre-filled pen only in those children that require a dose of 80 mg and do not require dose preparation. Taltz is not recommended for use in children with a body weight below 25 kg. Paediatric body weights must be recorded and regularly re-checked prior to dosing. **Psoriatic arthritis** Recommended dose: 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. Axial spondyloarthritis (radiographic and non-radiographic) Recommended dose: 160 mg (two 80 mg injections) by subcutaneous injection at Week 0, followed by 80 mg every 4 weeks (see SmPC for further information). For all indications consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks. **Elderly**: No dose adjustment required. Renal or hepatic impairment: Taltz has not been studied in these patient populations. No dose recommendations can be made. Paediatric plaque psoriasis (below a body weight of 25 kg and below the age of 6 years) There is no relevant use of Taltz in children below a body weight of 25 kg and below the age of 6 years in the treatment of moderate to severe plaque psoriasis. **Paediatric psoriatic arthritis** The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available. There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis Method of administration For subcutaneous injection. Injection sites may be alternated. If possible, areas of skin that show psoriasis should be avoided as injection sites. Must not be shaken. **Contra-indications** Serious hypersensitivity to the active substance or excipients. Clinically important active infections (e.g. active tuberculosis). **Warnings and Special Precautions Infections:** Treatment associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections. Should be used with caution in patients with clinically important chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If an infection develops, monitor carefully and discontinue if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves. Must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB. Hypersensitivity: Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration should be discontinued immediately and appropriate therapy initiated. Inflammatory Bowel Disease (including Crohn's disease and ulcerative colitis): Cases of new or exacerbations of inflammatory bowel disease have been reported (see SmPC). Ixekizumab is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, ixekizumab should be discontinued and appropriate medical management should be initiated. **Immunisations**: Should not be used with live vaccines. No data are available on the response to live vaccines: there are insufficient data on response to inactive vaccines. **Excipients**: This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially "sodium-free". (See SmPC for full information on excipients). **Interactions** Safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated. In population pharmacokinetic analyses, drug clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate. When Taltz was co-prescribed with drugs metabolised by CYP3A4, CYP2C9, CYP2C19, CYP1A2 or CYP2D6 in patients with moderate to severe psoriasis no clinically significant impact on the pharmacokinetics of these drugs was found. Fertility, Pregnancy, and Lactation **Women of childbearing potential:** Should use an effective method of contraception during treatment and for at least 10 weeks after treatment. **Pregnancy**: Recommended to avoid the use of Taltz during pregnancy. **Breast-feeding:** A decision should be made whether to discontinue breast-feeding or to discontinue Taltz. **Fertility**: The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility. Effects on ability to drive and use machines Taltz has no or negligible influence on the ability to drive and use machines.

taltz®
(ixekizumab)

OUR GOAL IS CLEAR. TOUCHABLE. SKIN.

After **1 WEEK** of treatment with Taltz, the average patient has

compared to baseline*

After **2 WEEKS** of treatment with Taltz, the average patient has

compared to baseline*

After **12 WEEKS** of treatment with Taltz, the average patient has

compared to baseline*

extract from Integrated Data Analysis of UNCOVER 2

Taltz, a targeted IL-17A inhibitor with high binding affinity (kd<3 pM) Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

* measured as percentage decrease in PASI score from baseline

Undesirable Effects **Summary of the safety profile:** The most frequently reported adverse drug reactions were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis). Injection site reactions: The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz. **Infections**: In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo. The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo. Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis. **Paediatric population:** The safety profile observed in children with plaque psoriasis is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of conjunctivitis, influenza, and urticaria which were common. Inflammatory bowel disease was also more frequent in paediatric patients, although it was still uncommon. Very common (≥ 1/10): Upper respiratory tract infection, injection site reactions. Common (≥ 1/100 to < 1/10): Tinea infection, herpes simplex (mucocutaneous), oropharyngeal pain, nausea. Laboratory assessment of neutropenia and thrombocytopenia In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, theblood neutrophil count was ≥1,000 cells/mm3. Such levels of neutropenia may persist, fluctuate or betransient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm3. In general,neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift froma normal baseline platelet value to <150,000 platelet cells/mm3 to ≥75,000 cells/mm3.Thrombocytopenia may persist, fluctuate or be transient.The frequency of neutropenia and thrombocytopenia in psoriatic arthritis clinical studies is similar tothat observed in the plaque psoriasis studies

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting, The Medicines Authority , Post-Licensing Directorate, 203 Level 3, Rue D'Argens, GŻR-1368 Gżira; www.medicinesauthority.gov.mt; postlicensing.medicinesauthority@gov.mt

Legal Category POM Marketing Authorisation Numbers and Holder EU/1/15/1085/001, EU/1/15/1085/004. Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.
Date of Preparation or Last Review June 2020 **Further Information is Available From** Charles de Giorgio Ltd Triq. Kan. Pirrotta B'Kara, BKR 114, Malta

This medicinal product is subject to additional monitoring. To report any suspected adverse reactions associated to this medicine is important.
Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies. For full prescribing information please refer to your local country product information.

VV code :PP-IX-MT-0014 date of preparation : 22/07/2020

reference:
1.Lilly DoF IXE014 2015 (v1.0)
2.Mease PJ et al Ann Rheum Dis 2020 123

DR MURIEL BELLIZZI

The use of Power Words when dealing with Chronic Pain

Keywords: Chronic pain, Communication, Quality of Life, Hypnosis, Powerful Words

ABSTRACT

What do the pain clinics and the sales business industry have in common? The answer to this is attention and engagement during a conversation. Hypnosis has taught us throughout the years that this type of inexpensive, non-pharmacological intervention and safe procedure can be used in clinics to engage better with the patient. The use of the first stage of hypnosis is particularly relevant, more specifically the use of power words which can help achieve better and more effective communication, leaving an empowered client.

1. INTRODUCTION

20% of the adult population in Europe are affected by chronic pain.[1] This means that one in five Europeans suffers from pain that has been present for more than 3 months. Chronic pain adds up to 1.5 billion adults' worldwide.[2] The most important factor of these figures is that pain has an impact on the quality of life of the individual.

Pain is one of the leading causes of years lived with disability according to the Global Burden of disease in 2017.[3] Consequently pain is not only an individual problem but also a hurdle to the health care systems and the economy. This burden to the patient and society costs up to $635 billion in the US[4] and €441 billion in Europe as stated by the Societal Impact of Pain.[5] These costs are greater than that of heart disease, cancer or diabetes.[3]

Pain, chronic pain in particular, is a very subjective symptom. Its complexity is since pain experience can be perceived and managed differently by each individual. Anxiety and stress usually co-exist with chronic pain which will increase sensitization to pain in certain areas of the brain, as well as increase cholecystokinin in blood which will act as an opiate antagonist. Further to this, stress hormones shuts down the dopamine systems which is the reward pathway.[6,7] Effective communication has always been of the utmost importance between a patient and the evaluating and managing pain physician. In keeping with this, having good communication skills helps in eliciting effective pain history and subsequent assessment leading to an accurate diagnosis and ultimately a patient-centred approach in a realistic treatment and management plan.[8] This will ultimately help in reducing pain, empowering and motivating patients, resulting in better quality of life.

2. HYPNOSIS

Hypnosis, also known as hypnotherapy, is a type of alternative non-pharmacological medicine that can alter the consciousness by suggestion. It was James Braid, a Scottish neurosurgeon, in the late 1800's that invented the word hypnosis from the Greek word 'Hypnos' meaning sleep. He is considered as the first hypnotherapist. This type of therapy has flourished over the past two decades and is now a well-established treatment for managing pain in the adult population.[9] It has been defined as a state of attentive and receptive concentration generating changes in individuals' experiences of themselves and their environment.[10,11]

Hypnosis usually, but not always, involves relaxation methods.[14] It allows the individual to move into the unconsciousness and alter any mental impairment and function better in the conscious state. The theory behind this therapy is confirmed with neuroimaging studies in adults undergoing hypnosis. These studies have shown that during hypnotic experiences significant changes associated with sensory and perception of pain are involved, namely the somatosensory cortex, thalamus and insula as well as the supplementary motor cortex.[13-15]

The use of hypnosis has been increasingly used in multidisciplinary pain management. Studies have shown that hypnosis helped alleviate pain and anxiety before, during and after surgical procedures, both invasive and non-invasive.[11,12]

2.1 Hypnosis and Chronic pain

The interest in the use of hypnosis in treating chronic pain is currently increasing. An increasing number of studies have been published with confirms that hypnosis can help in managing chronic pain more safely with less side-effects than pharmacological and interventional treatments. Hypnosis in chronic pain starts with a hypnotic induction which proposes relaxation. This is followed by post-hypnotic suggestions including targeted verbal ideas that will help alleviate pain even after the session. Teaching the patient self-hypnosis can also help the patient in daily pain reduction.

The largest meta-analysis to date investigating the effectiveness of hypnosis as a technique for reducing pain was published by Thompson et al. (2019) which gathered evidence from 85 controlled studies worldwide, from 1970 till 2017 consisting of 3632 participants (hypnosis n=2,892, control n= 2,646, with crossover trials primarily used).[18] This meta-analysis aimed to quantify the effectiveness of hypnosis for reducing pain and identify factors that influence efficacy. Trials were systematically searched comparing hypnotic inductions with no-intervention control conditions in relation to pain ratings, threshold and tolerance. 3632 participants were analysed. Pain relief was strongly influenced by the use of direct analgesic suggestion as well as hypnotic suggestibility. These findings suggest that hypnotic intervention can deliver meaningful pain relief for high and medium suggestibles and therefore may be an effective and safe alternative to pharmaceutical intervention. Overall, the findings that hypnotic induction resulted in a reliable decrease in experimentally-induced pain suggest that hypnosis may represent a potentially effective and safe alternative or adjunct to pharmacological intervention for acute pain.[18]

2.2 The 4 stages of hypnosis

James Braid, in the 1800's describes the 4 basic rules required for a patient to reach a subconscious stage where one is able to alter the conscious mind as shown in table 1.

2.3 How can we use the first stage of hypnosis to achieve better communication?

The use of power words are an integral part in the first stage of hypnosis. These will unknowingly captivate the patient's attention. These words especially though repetition will make the patient feel empowered. Although these powerful words may sound natural in everyday use, such words, when used in the correct environment and at the appropriate time, will help the clinician to engage better with the patient and also, in this first stage, the patient will be able to express himself and understand the facts more effectively.

Obviously, this can vary from one individual to another but there are observable patterns in the way we communicate verbally that can allow us to envisage typical actions.

The knowledge of powerful words and their use in the correct setting is a skill which can be learnt. These are used frequently in the sales industry and are taught to representatives to market their product i.e. engaging with potential clients'.

3. POWERFUL WORDS

"Imagine if communication with patients is more successful. **And you** can **remember** a time when it was natural to get a message across the patient without any problems. This is **because** you already know how…"

I have already used five power words to keep you reading.

These five powerful words that any individual can be associated with and trigger certain behaviour are the following:

3.1 'Imagine'

The word imagine immediately switches on imagination in an individual in which everything is possible in the subconscious mind. The use of their imagination helps explore options, limits and possibilities that they could have never considered before in reality. If this vivid imagination is done once, it is easier to do it again as this would have been also memorised too. This is an outstanding way of getting through resistances that occurred in the past and are memorized. Vivid imagination and reality is something that the brain can little differentiate between, so by actually switching on their imagination one can sense the feeling of being there and start exploring any answers or sensations. This allows us to be much more open to new ideas and lowers our guard.

3.2 'And'

The word 'and' automatically connects two ideas, that do not have to be related but will create a cause and effect situation or imply similarity. By linking these ideas, the first concept would be accepted more easily, and the second concept is likely to be received in a favourable way too. An example of such case would be: 'We can do physiotherapy and injections for this type of pain to improve'.

3.3 'You'

'You' or 'yours' immediately gets the individual's attention and directly activates the subconscious; which is where most of our decisions are made. This is even more empowered

Table 1: The 4 stages of hypnosis and their significance

Stage 1 - Absorb attention	Attention and focus are captured by speaking and engaging with the patient.
Stage 2 - Bypassing the Critical Faculty	Critical Faculty is the area of the brain used for reasoning and logic.
Stage 3 - Activate an unconscious response	Unconscious responses are activated leading to a hypnotic state.
Stage 4 - Leading the unconscious to desired outcome	Once all 3 states have been surpassed, the hypnotherapist is able to use hypnotic suggestions, in the form of commands and metaphors.

by using their own name, but it should not be exhausted and over-used since it may be interpreted as deceitful. Our name is the most familiar sound we have ever heard and it is acceptable, prior to the start of the session, for the hypnotist to ask how it is pronounced and then use it during the hypnosis to communicate effectively. This creates a very personal connection, based on trust and perceived environmental familiarity, which will ultimately raise the level of interest, becoming more open to shared ideas.

3.4 'Remember'

Reminiscing events from the past can make an individual able to remember events. If these are positive ones one can embrace and recall positive feelings such as love, friendship and enjoyable events that may help the individual reconnect with the positive moment. This may positively enhance their mood and then remove any negative feelings. You are not asking the individual to do anything, but you are asking them to remember and move to other situations where they have been more resourceful. An example is, 'Remember how much fun you had with your friends when you attended that meal?' Obviously, these statements would have been corroborated before the session.

3.5 'Because'

'Because' is a word where one is implying that there will be an explanation that follows. The reason that follows the 'because' should be brief, quick to respond and will work best for small requests or suggestions. Larger requests may not be able to surpass the critical factor in the brain and may not be accepted. An example of such case would be: 'weight loss in your case is ideal in treating back pain because there is arthropathy of the facet joints' instead of just saying 'you should lose weight.'

If no reason is suggested or even worse the over-used parentalistic statement 'because that what's needs to be done' will immediately shut the individual from listening and involving more in the conversation.

Example: taking these medications will help you sleep better because you have a sleeping problem' instead of saying 'Take this treatment because that what's needs to be done'.

When this lacks in communication, the individual will start looking for reasons and this will ultimately lead to more resistance. Therefore, by using the word 'because' followed by a reason, this will immediately fill that gap and the individual will recognise that reason and is able to take subsequent action.

4. CONCLUSION

Increasing concern over the side-effects, addictive properties and costs of opioid medication has led to an urgent need to identify non-pharmacological interventions for pain that are effective and safe. Hypnosis has confirmed that there is a place for this well-established integrative, inexpensive, non-pharmacological intervention for chronic pain management in adults; there is also a growing research interest in the management of chronic pain in the paediatric population.[19,20]

Hypnosis can change the way how individuals behave and think. By altering very little one can achieve great results and the use of powerful words will ultimately help in becoming a better communicator. Communication starts by building trust your product (in the case of selling items) or services (in clinics)

DISCLOSURES

There are no conflicts of interest to declare.

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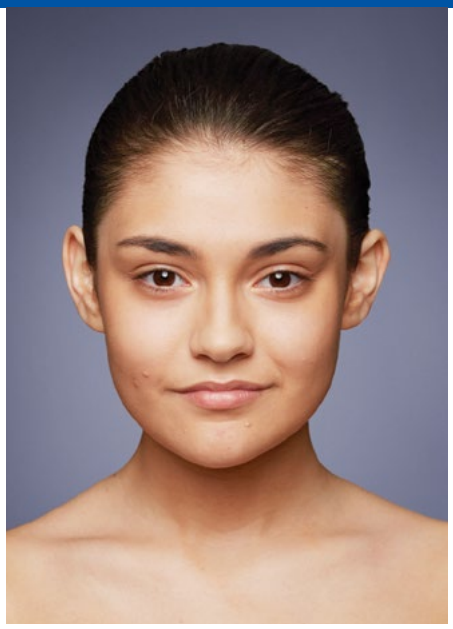
DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST[1,3]



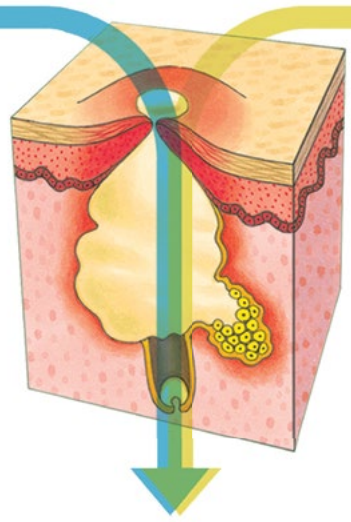
DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

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

Clindamycin

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



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

DUAC UNDERSTANDS WHAT'S IMPORTANT TO PATIENTS

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

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

DUAC INDICATIONS & USAGE ADVICE[2]

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

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

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

• Thoroughly wash the affected area of skin

• Gently pat dry

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

TIPS[4]

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

DUAC ONCE DAILY GEL 10mg/g + 50mg/g ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: Duac Once Daily Gel 10mg/g + 50mg/g. **ACTIVE INGREDIENTS:** Clindamycin phosphate/anhydrous benzoyl peroxide. **PHARMACEUTICAL FORM:** Gel. **INDICATIONS:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **POSOLOGY:** Adults and Adolescents (12 years and over): Once daily (evening) to affected area. Should not exceed more than 12 weeks. Applied in a thin film after washing gently with mild cleanser and fully drying. Was hands after application. **CONTRAINDICATIONS:** Hypersensitivity to active substances/lincomycin/excipients. **PRECAUTIONS:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Caution in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, atopic patients, concomitant topical acne therapy. Increase in peeling and reddening will occur in most patients during first few weeks of treatment. If severe local irritancy, discontinue. Prolonged exposure to sun should be avoided. In patients with sunburn, this should be resolved before use. If significant diarrhoea/abdominal cramps occur, discontinue (symptoms may indicate antibiotic-associated colitis). May bleach hair or coloured fabrics. Patients with a recent history of systemic or topical clindaymcin and erythromycin are more likely to have pre-existing anti-microbial resistant Propionibacterium acnes and commensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY /FERTILITY / LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. Lactation: should not be applied to breast area. **UNDESIRABLE EFFECTS:** Very common (≥1/10): erythema, peeling, dryness. Common (≥1/100 & <1/10): burning sensation. Refer to the SPC for full list of undesirable effects. **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA192/02801. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Ltd. Legal Category: POM. **Date of Preparation:** May 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). Malta: Cases may also be reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

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Stiefel
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For more information
https://gskpro.com/en-mt/products/duac/

Duac once daily gel
Clindamycin 1% and benzoyl peroxide 5%

Job no.: PM-MT-CBP-ADVR-19001 Date of preparation: November 2019

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

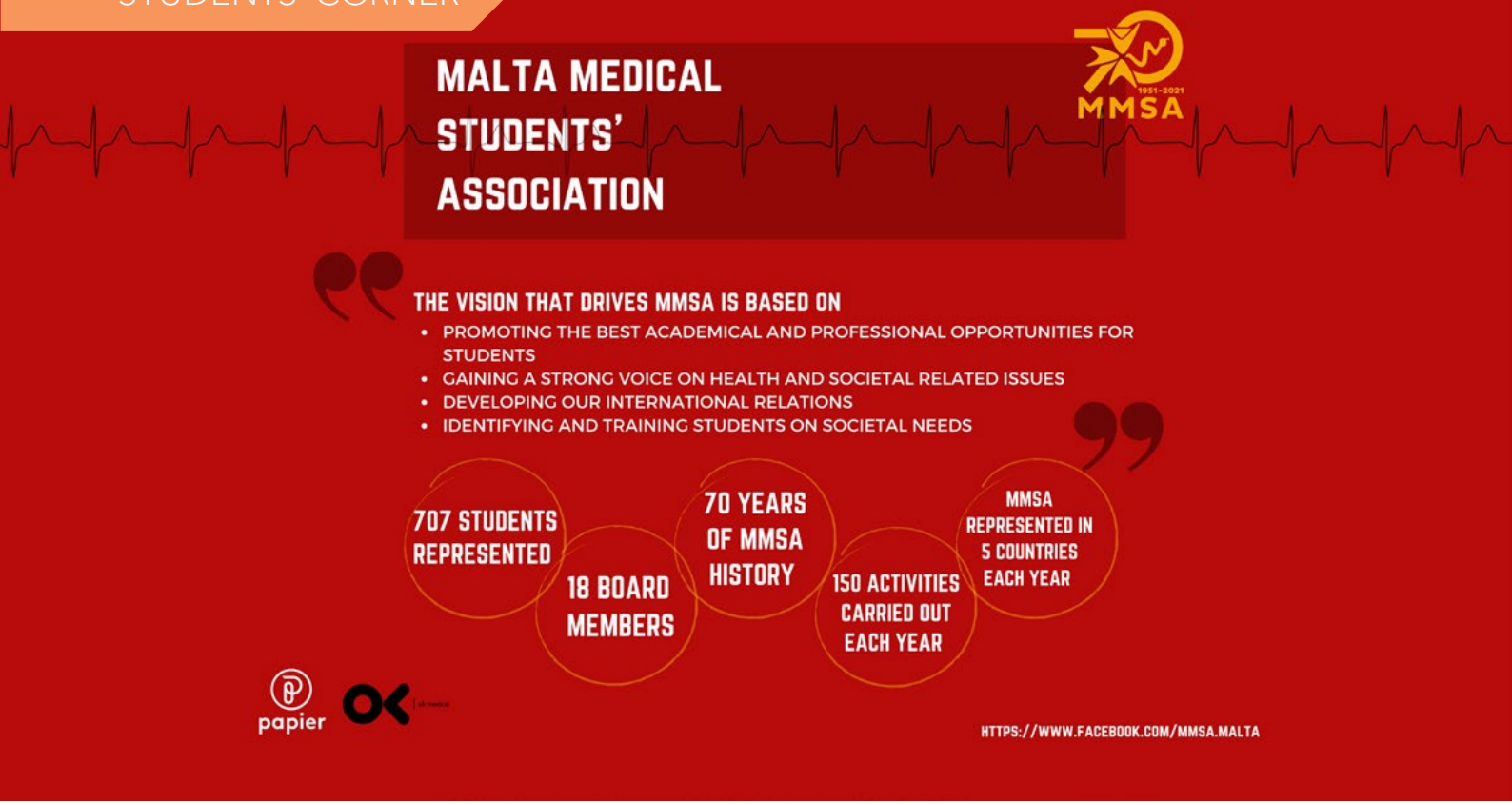
Date of preparation: April 2020

Lundbeck

Deborah Campbell
dcampbell@charlesdegiorgio.com
Mobile: 99406130

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

Brintellix® vortioxetine



The Role of

Pharmacy Students during the COVID-19 pandemic

MALTA PHARMACEUTICAL STUDENTS' ASSOCIATION

Pharmacy and Pharmaceutical Technology students from the Department of Pharmacy at the University of Malta were involved in several activities during the COVID-19 pandemic in Malta. During such a time, students are encouraged to engage in healthcare activities, in preparation for their professional life. Students were particularly involved in two main activities which required manpower.

Students were invited by the Pharmacy of Your Choice Unit to assist with the +70 Domiciliary Delivery Service. Their task was to deliver medicines to older and vulnerable persons who were encouraged by the health authorities to stay at home. Together with the Local Enforcement System Agency, students delivered POYC medicines to these persons' doorstep. The responsibility of the students was to deliver the right medicines to the respective patient. This was a win-win situation to both Pharmacy students and patients. Such an activity enhanced the relationship between the future healthcare professionals and the patients and at the same time decreased the patients' need to visit healthcare centres or community pharmacies.

Pharmacy and Pharmaceutical Technology students were also invited to prepare hand rub sanitisers at the Pathology Department of Mater Dei Hospital in collaboration with the Central Procurement and Supplies Unit. This, in view of the fact that demand for hand rubs by healthcare workers increased during the pandemic.

Although Pharmacy students practise at community pharmacies as part of their training, some students increased their presence at this time of need. As front-liners, this was very challenging. Apart from assisting the pharmacist, they were also involved in educating the patient. Students explained to patients the correct way how to apply hand sanitisers, how to wear masks properly, and how to practise social distancing amongst others.

During this time, students continued following on-line lectures and working on their assignments. Like all other students at the University, they faced the uncertainties related to the examination period.

Although the situation is not yet over, pharmacy students are still aware of the potential re-emergence of the virus. For the time being the situation has eased, however, pharmacy students are there on-call.

Dr Natasha Azzopardi-Muscat, a brilliant public health consultant, discusses with Dr Ian Ellul her views on the relationship between politics and health, gender equality, as well as her new role at the WHO.

A Maltese Medic in Copenhagen

YOU HAVE OCCUPIED VARIOUS HEADSHIP POSITIONS WITHIN THE MINISTRY OF HEALTH AND YET YOU HAVE ALWAYS SEEMED TO MANAGE EFFECTIVELY YOUR WORK, RESEARCH PROJECTS AND ACADEMIC COMMITMENTS. WHAT IS KEY TO THIS, CONSIDERING THE FACT THAT YOU HAVE A BUSY FAMILY?

I do love travelling, swimming, the theatre, going to Gozo, as well as attending activities with my three children but the rest of my waking hours I simply work! So, my answer to your question is that it is key to have support. I readily admit to being a workaholic but I have been fortunate as my parents and my husband, himself also a doctor, have provided presence and stability to the children over the years during my long working days and travels although I still tend to coordinate everyone's timetables remotely.

YOU ARE A FOUNDING MEMBER OF THE MALTESE ASSOCIATION OF PUBLIC HEALTH MEDICINE AND HAVE BEEN ALSO PRESIDENT OF THE EUROPEAN PUBLIC HEALTH ASSOCIATION. WHY SPECIALISE IN PUBLIC HEALTH?

I guess the answer can be traced to my summer internship in the UK when I was a 4th year medical student at King's College. I loved walking over Westminster Bridge with the Houses of Parliament on one side of the Thames and Guy's and St Thomas' on the other. One day, I vividly remember asking myself … which direction should I follow? Although I loved clinical work with patients, I was increasingly drawn to politics through my activism in student and youth organizations as I was discovering that in politics you can affect the lives of so many people with just one single decision.

That seed was subsequently nurtured by the late Prof. Herbert Michael Gilles - born to Maltese parents in Egypt and eventually becoming a visiting lecturer to the University of Malta. I learnt to appreciate that public health effectively weaves the clinical knowledge with one's ability to put forth political decisions that affect the health of people.

So to me, Public Health quintessentially means pacing Westminster bridge …something I have done incessantly for the past two decades. It entails bridging two separate worlds; leading health services with clinicians whilst concomitantly engaging with politicians to ensure effective decision-making to protect, promote and invest in people's health.

BETWEEN 2011 AND 2013 YOU WERE APPOINTED AS CHIEF MEDICAL OFFICER, THE FIRST WOMAN TO ACTUALLY OCCUPY THAT POST. DID THIS CREATE RIPPLES?

By the time I was appointed Chief Medical Officer I was a seasoned face at the Ministry of Health. However, ten years earlier, in 2001, when appointed as Director EU & International Affairs, at age 27 I was the youngest director ever,a woman and to top it all … 8 months pregnant. My onerous obligations included participating in inter-ministerial meetings at the Office of the Prime Minister in the run-up to Malta's accession into the EU. I found myself amongst 12 men with a median age somewhere between 40 and 50 years. That period was challenging, but diffidence gave way to comradeship and support; and I treasure those memories fondly to this very day. Fast forward to 2020 and I can boldly say that in the health sector, many key leadership positions are now held by women.

WHO ARE YOUR ROLE MODELS?

Undoubtedly, Martin Mckee, P*rofessor* of Public Health at the London School of Hygiene and Tropical Medicine. For the last 23 years he has been my colleague, mentor and friend. He is highly intelligent but humble to the core at the same time, a rare find nowadays ... always available to mentor students and early career professionals. I was tremendously fortunate since when I was at the London School of Hygiene and Tropical Medicine in 1998, he asked me to write the first WHO Health Systems in Transition report for Malta, my very first publication. Many years later, having worked closely together on several projects, he encouraged me to contest the election to become his successor as President of the European Public Health Association

Another person who influenced me profoundly is Dr Gro Harlem Brundtland, who served as Director-General of WHO between 1998 and 2003. In 1999, as a junior public health doctor working at the Ministry of Health, I was informed that I would form part of Malta's delegation to the World Health Assembly in Geneva just a few days before the event. This, I got to know later, was precipitated by a policy decision by Dr Brundtland strongly recommending that if a country delegation had more than three people, at least one had to be a woman.

I have never met Dr Brundtland yet, her lifetime achievements inspired me. Apart from being DG of WHO and previously Prime Minister of Norway, she remains well known for her early contribution to sustainable

development … and had four children! ... making me realise that it was possible to reach the highest positions, exert global influence and yet also be a mother.

HOW DO YOU VIEW THE RELATIONSHIP BETWEEN PUBLIC HEALTH AND POLITICS?

Health and a country's wealth have a symbiotic relationship. COVID-19 has triggered much debate on whether health or the economy should prevail. In practice it has taught us clearly that we cannot have one without the other. But most of all, that economic and health experts should realise better that economic growth and health are in themselves both means to an end … a fulfilled and dignified lifetime where well-being plays a central role. GDP is the most important economic indicator for a country. Yet, is it a good enough measure of a country's progress? Complementing GDP with social indicators related to quality of life and well-being, as well as environmental indicators has been advocated as an alternative way to actually measure the real wealth of a country.

IN YOUR OPINION WHAT ARE MALTA'S CHALLENGES WHEN IT COMES TO SOCIAL DETERMINANTS OF HEALTH?

In recent years Malta registered progress in reducing overall tobacco consumption, as well as alcohol use in 15-year olds. However, we still are facing formidable challenges with obesity and diabetes as well as air pollution. In keeping with this the Maltese Association of Public Health Medicine has submitted various proposals to better regulate unhealthy foods and to increase walkability in Malta.

One must appreciate that those groups which are most adversely affected by obesity, exposure to air pollution and tobacco use and adverse mental health - are those who have the least education, lowest incomes and lack job skills. Health inequalities and the wider determinants of health need to be addressed far more vigorously if we want to continue to make effective progress in health, the economy and society.

LAST MAY YOU WERE APPOINTED DIRECTOR OF THE DIVISION OF COUNTRY HEALTH POLICIES & SYSTEMS AT WHO. WHAT LIES ON YOUR AGENDA?

Reflecting on the role of health systems, health and society to better shape a post-COVID world is an opportunity not to be missed. There are various areas which need to be addressed. Championing collaboration between member states with a view to gain access to better and cheaper medicines is one of them. Another area relates to transforming sustainable health service delivery and addressing the healthcare workforce shortage amongst the 53 countries within the WHO European region. Digital health enablers play an important role in this. Even locally, is there a need for patients, including elderly ones, to visit hospital to receive investigation results when these require little or no intervention? Can't this be done via telemedicine? Another priority area is mental health where the European Region has a significant disease burden and much more needs to be done from a political perspective as well as service transformation.

YOU ARE NOW BASED IN COPENHAGEN, RIGHT? FOR HOW LONG?

I have now moved to Copenhagen. My contract runs until May 2021 and may be renewed. We will take it from there one step at a time

YOU ARE NOT THE ONLY MALTESE PERSON TO HOLD A PROMINENT ROLE WITHIN THE WHO. DR GAUDEN GALEA, WHO'S REPRESENTATIVE IN CHINA, FEATURED PROMINENTLY DURING THE PANDEMIC. ARE YOU FOLLOWING HIS STEPS?

Dr Galea, founder of The Synapse, has been my friend and mentor for many years. We have always been in contact. Since 2013, I completed my PhD, subsequently became president of the European Public Health Association, and have always been the sort of person to ask myself what next now? Dr Galea encouraged me and was key in my decision to apply for the post of Director of the Division of Country Health Policies & Systems at WHO.

WHO IS CURRENTLY FACING BIG CHALLENGES, MOST NOTABLY RELATED TO FUNDING. THE US - THE BIGGEST FUNDER CONTRIBUTING MORE THAN $400 MILLION IN 2019 – HAS RECENTLY ANNOUNCED THAT IT WILL STOP FUNDING. THE BILL AND MELINDA GATES FOUNDATION, ALSO BASED IN THE US, ARE THE SECOND BIGGEST FUNDERS - MORE THAN THE UK AND NORTHERN IRELAND PUT TOGETHER - CONTRIBUTING OVER $200 MILLION. WHAT ARE YOUR VIEWS ON THIS?

The US government has been a very strong and important partner for WHO since inception. WHO is working with several partners for proper forward planning.

WILL YOUR CHILDREN FOLLOW YOUR STEPS?

Our elder son is reading architecture, our daughter loves the performing arts and is increasingly drawn to international affairs; possibly our youngest son could become a doctor. I always advise them to choose a career which they love doing … because this means that work will not be a burden but something that gives them joy.

I READ THE SYNAPSE BECAUSE ....

The journal has improved considerably under your stewardship. My family likes to read it since it provides an insight in research being conducted locally. It is also the only local medical publication which we still physically receive at home and ends up lying around on the kitchen table for a few days so it is very convenient for us to read. Keep up the good job!

The views and opinions expressed in this interview are solely of the interviewee and do not necessarily reflect the official policy or position of WHO.

DR PIERRE VASSALLO

Imaging Back Pain – Part 1

Managing back pain is often a complex diagnostic and therapeutic challenge because of the wide variety of causes.

While direct neurological impingement by a herniated disc or bone is a frequent cause, inflammatory disease, and associated inflammation-inducing cytokines also play a highly active role in generation of back pain.

The following article will discuss microscopic and macroscopic mechanisms that lead to back pain, as well as MRI imaging clues that help identify these mechanisms.[1] Knowledge of these mechanisms and the ability to detect them through imaging findings help guide clinical management of back pain.

Back pain is one of the most common clinical problems worldwide. It is estimated that back pain affects up to 10% of the global population at any given time.[2] It causes considerable economic burden on individuals, families, employers, and the state.

There are two mechanisms causing back pain: mechanical (macroscopic) and non-mechanical (microscopic). Back pain may also be classified based on the anatomical location as (a) discogenic pain, (b) neuropathic pain, (c) osseous pain, (d) facetogenic pain and (e) paraspinal/myofascial pain.

Part 1 in this three-part series of articles will deal with the complex subject of the causes of discogenic pain with special reference to MRI findings that help us understand the pain mechanisms and guide management.

DISCOGENIC PAIN PATHWAYS

The intervertebral disc is composed of a central gelatinous core (nucleus pulposus) and a retaining peripheral fibrous capsule (annulus fibrosus). Macroscopic mechanisms causing discogenic pain include disc disruption, annular fissures, disc bulging, protrusion, and extrusion. Microscopic discogenic pain mechanisms stem from innervation and/or neovascularisation of the degenerated disc.

DISC NERVE SUPPLY AND NERVE-MEDIATED PAIN

The intervertebral disc and adjacent structures receive their sensory nerve supply through the sinuvertebral nerve, which is a recurrent nerve that originates from the spinal nerve outside the neural foramen and follows a recurrent course back into the spinal canal taking sensory branches from the posterior annulus fibrosus, posterior vertebral body, periosteum and ventral meninges (Fig 1). The anterior annulus, anterior vertebral body and periosteum take their sensory supply from the sympathetic chain of ganglia and interconnecting lumbar nerve plexus, which in turn communicates with the sinuvertebral nerve via the gray ramus communicans.

Ascending and descending branches of the sinuvertebral nerve and lumbar plexus connect multiple levels, so that is it frequently difficult to identify the level of the source of pain.[3] In addition, the sinuvertebral nerve is composed of mixture of somatic and autonomic nerves, so that the nature of symptoms resulting from a disc disease may be quite varied.

Nociceptors are specialised neurones (single nerve fibres) that convert any process that causes tissue damage into electrical impulses that are transmitted to the higher centres of the brain. At the central level, second order neurones transmit impulses from the mesencephalon and thalamus to the somatosensory and anterior cingulate cortex, respectively. These second order neurones are susceptible to central sensitisation, which increases their excitability causing abnormal responses to normal inputs. These mechanisms are responsible for chronic and psychogenic pain.

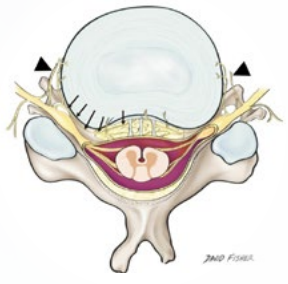


Figure 1: The sinuvertebral nerve (arrows) provides sensory function to the annulus and adjacent structures via recurrent branches that enter the intervertebral foramen and via the gray ramus communicans (arrowhead) that connects it to the lumbar nerve plexus.[3]

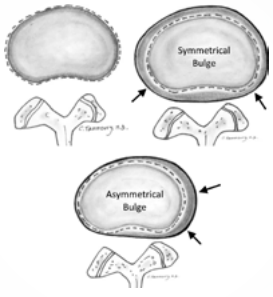


Figure 2: Diagram showing the difference between a symmetrical and an asymmetrical disc bulge. Disc bulges may result in intrinsic pain due to stretching of the annulus fibres. However, dorsal, and lateral disc bulges may also impinge on neurological structures causing neurogenic pain.

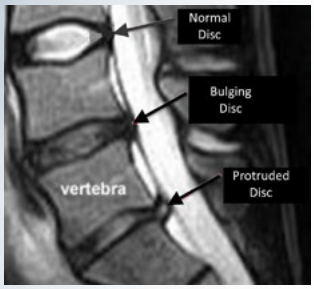


Figure 3: Sagittal scan through the L3-S1 disk levels, showing a normal disk (L3/4), a bulging disk (L4/5) and a disk herniation (L5/S1).

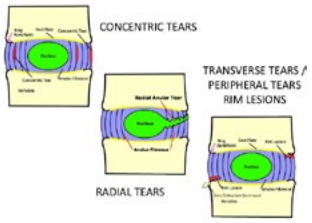


Figure 4: Diagram showing the difference between concentric, radial, and transverse /peripheral / rim tears.

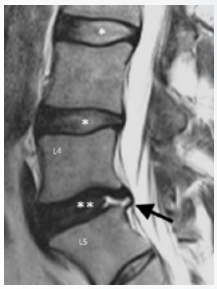


Figure 5: Sagittal T2-weighted MRI image of the lower lumbar spine showing an annular fissure (arrow) at L5/S1 level. Also note that healthy discs present at higher levels show high T2 signal in the nucleus pulposus matrix (*), while there is low signal in nucleus pulposus of L5/S1 (**).

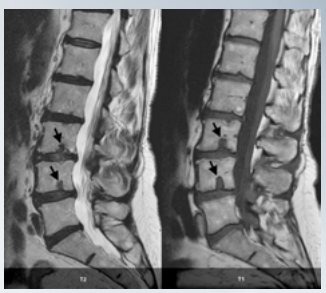


Figure 6: Sagittal T1- and T2-weighted MR images of the lumbar spine showing intravertebral disk herniations or Schmorl's nodes (arrows).

Discogenic pain may arise from damage to the outer layers of the annulus that contain pain receptors, which transmit pain stimuli through the sinuvertebral nerves.

DISCOGENIC CYTOKINE AND IMMUNOLOGICALLY MEDIATED PAIN

Annulus tissue damage can cause pain and inflammation by inducing the release of pain-inducing cytokines and their by-products. Steroids, non-steroidal anti-inflammatory drugs and injectable local anaesthetic agents, control pain by blocking chemical pathways that generate these pain-inducing substances.

Finally, the nucleus pulposus is isolated from the immune system and is recognised as one of the "immunologically privileged" tissues. A tear in the annulus will allows the nucleus pulposus to come in contact with macrophages, which in turn release inflammatory mediator substances.

DEGENERATIVE DISC DISEASE

Degenerative disc disease accounts for 39% of cases of chronic low back pain. The pain is non-specific, non-radicular and occurs in the absence of spinal deformity or instability.[4] It results from degradation of the extracellular matrix of which the nucleus pulposus is composed. The matrix degeneration is caused by a decrease in generation of new and healthy matrix and an increase in matrix degrading enzymes.[5]

Cytokines and other inflammatory/immune mediators such as Interleukin 1 (IL-1) and Tumor necrosis factor alpha (TNFα) released by the damaged disc contribute considerably towards discogenic pain, however they are also likely to be responsible for triggering disc repair mechanisms.[6]

The degradation of the nucleus pulposus seen in degenerative disc disease results in a reduction in disc height and volume as well as loss of hydrostatic pressure within the disc. This leads to a transfer of load bearing from the nucleus pulposus to the annulus fibrosus. Tensile strains occurring within the annulus fibrosus result in damage to its collagen fibres. Changes within the annulus fibrosus account for most of the findings seen on MRI relating to disc degeneration. Table 1 lists the findings seen on MRI that relate to damage in the annulus fibrosus in order of severity.

Table 1. MRI Findings of disc degeneration:

1. Disc Bulge
   a. Symmetrical
   b. Asymmetrical
2. Annular Fissures
   a. Concentric (Type 1)
   b. Radial (Type 2)
   c. Transverse (Type 3)
3. Disc herniation
   a. Protrusion
   b. Extrusion
   c. Sequestration
   d. Migration

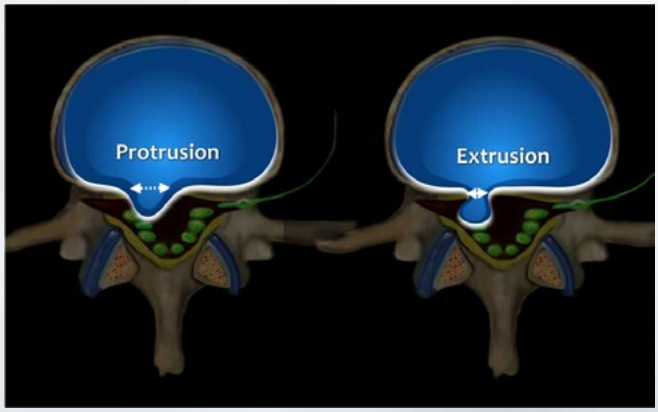


Figure 7: Diagrammatic representation of a disk herniation; when the diameter of the neck of the disk herniation constitutes its largest diameter, the herniation is considered a protrusion; when the neck diameter is smaller than the diameter of the herniation, this constitutes a disc extrusion.

Figure 8: Loss of contact (arrow) of the herniated nucleus pulposus from the nucleus pulposus located within the main intervertebral disc space constitutes a disc sequestration.

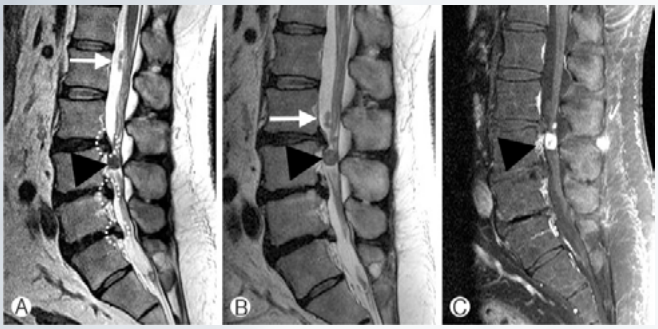


Figure 9: Disk migration. A. Sagittal MRI scan of the lower lumbar spine showing multiple disk extrusions (dotted circles). There are two sequestrated discs; a smaller sequestrum (white arrow) has moved from the level of L2 to L3 as noted in B taken a few days after A; a larger sequestrum (arrowhead) shows marked contrast enhancement on the contrast enhanced T1-weighted scan (C). Note that there is also contrast enhancement in the adjacent soft tissues resulting from an inflammatory reaction to the sequestrum.

DISC BULGING

A bulging disk occurs when the annulus fibrosus protrudes beyond the margins of the vertebral apophysis. Bulging may be symmetrical or asymmetrical (Fig 2). It therefore encroaches on space normally reserved for neural structures such as the spinal cord, the cauda equina or the segmental nerves in the intervertebral foramina.

Disc bulging is caused by loss of nucleus pulposus height/volume and by weakening of the annulus fibrosus. In a bulging disc, there is no leakage of the nucleus pulposus through the annulus fibrosus. Once the nucleus pulposus has leaked through the annulus fibrosus, this constitutes a disc herniation (Fig 3). Annular tears are a prerequisite for disc herniations.

DISC ANNULAR FISSURE

Previously annular fissures were referred to as annular tears; however, the term tear might imply trauma as a causative factor. However, tears are separations between the annular fibres or of the annular fibres from their attachments, which may occur in the absence of identifiable trauma.

There are three types of annular fissures: Concentric, radial, and transverse (rim lesions) (Fig 4).

Annular fissures appear as hyperintense foci within the annulus on T2-weighted MR images (Fig 5). Leakage of disc matrix into the annulus results in pressure on the nerve endings within the annulus and causes release of inflammatory/immune mediators that stimulate the same nerves.

However, linking an annular fissure noted on an MRI scan with the onset of the patient's pain may not be so simple. The fissure is often present before the time of imaging and before the patient's pain begins.

Interestingly, a type 3 (or peripheral/rim) annular fissure appears to be a requisite for a painful disk. It is uncommon for disks to be painful if they only show type 1 and/or 2 annular fissures and no type 3 fissures.[7]

DISC HERNIATION

Once the nucleus pulposus has leaked through endplates or through the annulus fibrosus, this constitutes a disc herniation.

Herniations through the superior or inferior endplates are called intravertebral disc herniations (Fig 6). These herniations are also known as Schmorl's nodes. They are thought to occur through natural weak points within the vertebral endplate created by perforating nutrient vessels.

Herniations through annulus are classified based on the size of their communication with the main intervertebral disc.

If the diameter at the base (annular side) of the herniation is its widest dimension, this represents a disc protrusion. When the diameter at the base of a disc herniation is narrower than its largest diameter, it is classified as a disc extrusion (Fig 7). When the extruded nucleus pulposus loses its connection with the disc space, it is considered a disc sequestration (Fig 8). Sequestrated disc material may migrate to another location (usually superiorly or inferiorly) (Fig 9).

The degree of inflammatory response to a herniated disc is visible on contrast enhanced T1-weighted MRI scans (Fig 9). This inflammatory reaction, which is one of the mechanisms responsible for causing pain, also leads to resorption of the herniated disk/sequestrum and contributes towards the healing process.

*In Part 2 of this series, we will discuss the **osseous** back pain, its mechanisms and MR imaging findings.*

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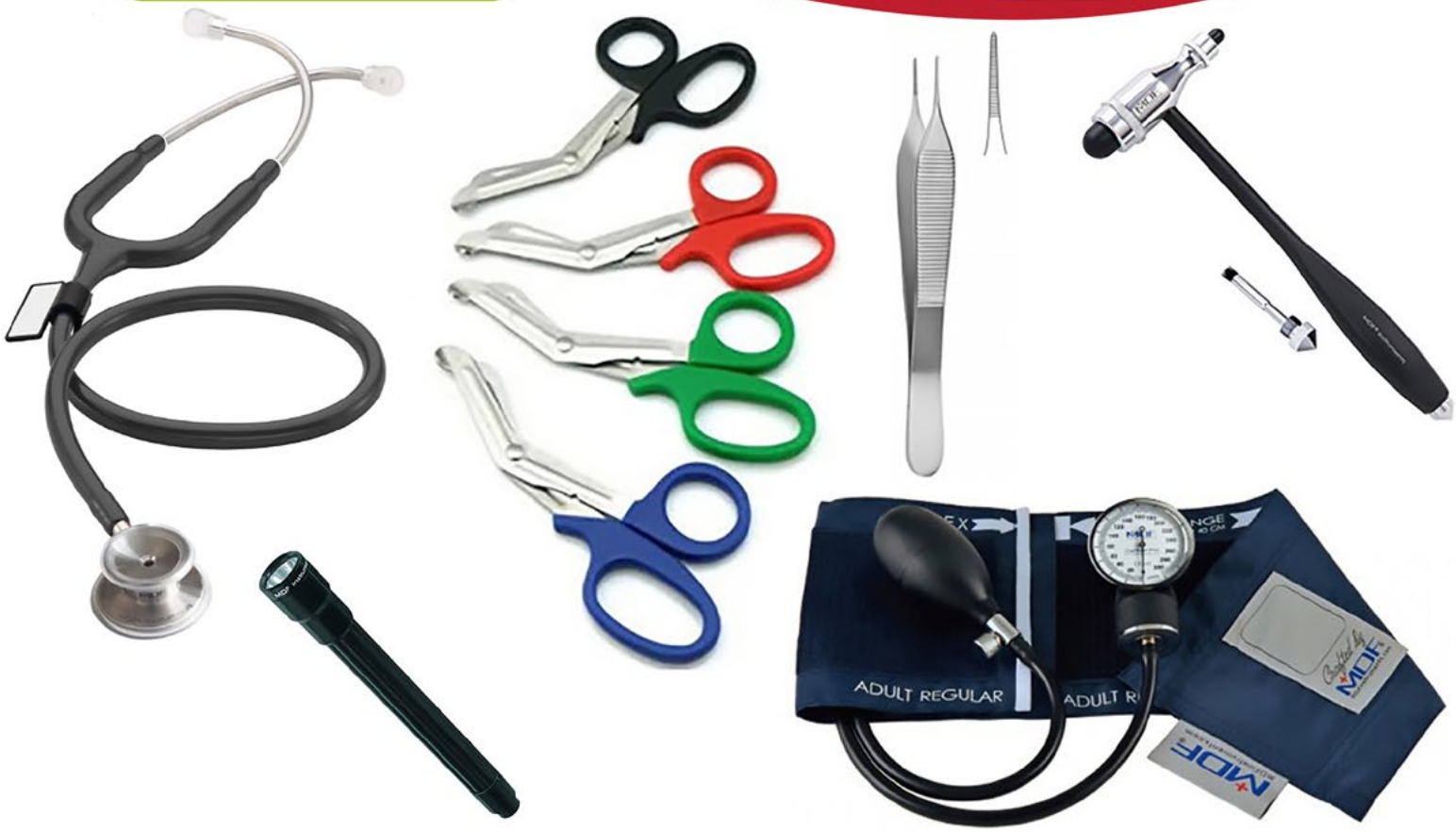

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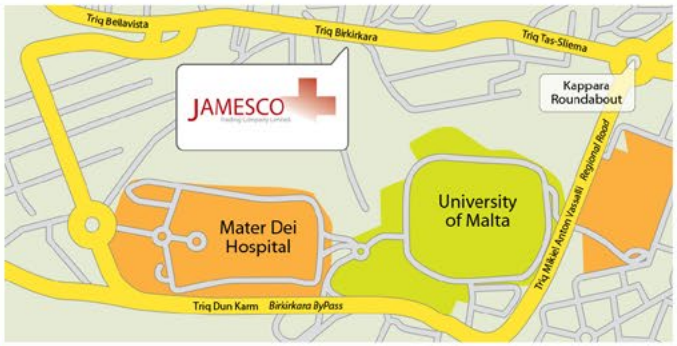

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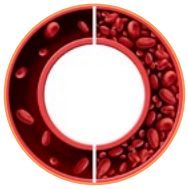

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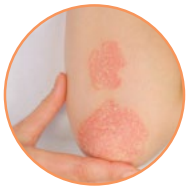

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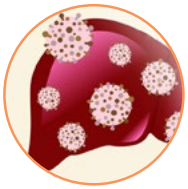

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