

# The Synapse

*The Medical Professionals' Network*

Issue 01/13

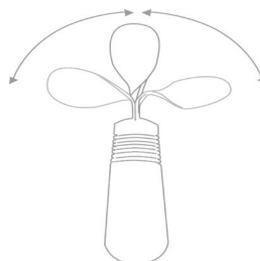
PRIMA **07**

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# Election review... on physical activity & electricity bills

In a few days time we will be having our general election. Obviously all three parties are promoting those candidates which in their opinion are the most suitable to woo those floaters who will ultimately determine which party will lead the country for the next 4-5 years. Funnily enough I have recently even witnessed agnostics starting to attend the church. Upon investigating I overheard one of them saying to another, something like "There is a God after all! ... everything which is possibly good for the society is going to be [miraculously] implemented during the next 5 years ... defying history, one must add ... but this is another story." However this article will put aside this all this bla bla bla and focus instead on some interesting facts linking elections to our own (and our patients') health.

Well, elections are not good for our health (it goes without saying, unless you are related to some candidate), especially the current one since we have been experiencing one of the longest campaigns ever. Election periods can have a direct or indirect negative effect on our health. During the voting period, we tend to experience a rise in CRF, cortisol and epinephrine which increase our blood pressure which in turn augments the overall risk for cardiac and cerebrovascular events. After the election results are published we also experience different settings which however pose a common risk ... a negative effect on our population's health, most notably the cardiovascular

system, albeit one is more of an acute nature than the other.

On one hand we see people celebrating intensely, often with excessive drinking and eating which could easily land them in our emergency department, and on the other hand, for the losing party supporters, we may see increased signs of post-election depression, even sub-clinically. One must also be aware that post-election depression may also lead to a relapse from past problems or conditions such as alcohol, drugs or mental problems. Other reported factors which are also sources of hospitalisation during election periods include traffic accidents, fights, occupational injuries and domestic violence. People also tend to refrain from being operated on the election day, obviously where it is considered possible. However fortunately for us, we do not have those long voting queues which we see abroad, so Maltese citizens do not run the risk of skipping meals (have I already state that there is God after all?), or their daily medication. The latter has also been reported as negatively affecting our health on the election day.

Interestingly, nearer to us, a study measuring the impact political elections have on the heart was carried out during the 2008 general election. The study spearheaded by Dr Mark Sammut revealed that the number of people admitted with acute cardiac coronary events during the election period was 184 (compared to 127 during the Euro

2008 football championship and 117 and 130 during the quieter control periods). Furthermore, there were 25 people who died of a heart attack in the week after the election, compared to 13 deaths during the Euro 2008 and 12 each in the other two quieter periods. It will be quite interesting to repeat the study during this election for comparative reasons.

So it is of the utmost importance to advice regular exercise, adequate water intake as well as some time to unwind at the end of the day for all our patients, but especially for those who we know are involved in campaigning. These preventive measures should be balanced by an increased awareness from our end for possible warning signs of depressive states shown by patients during visits following the election period such as increased anxiety, reported mood swings, insomnia etc.

And continuing with the election talk we have also included two related articles. One focuses on the positive impact which physical activity can have on mental health. And with the hot debate on the cost of electricity we could not resist the temptation of publishing some ideas on how businesses could save on electricity bills ... in fact inside this issue there is an academic article by Coleiro et al on how an estimated €580 can be saved during the summer months by local pharmacies ...enjoy! 

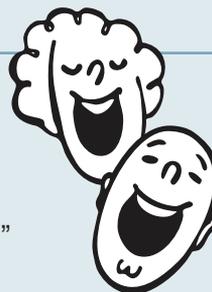
*Ian C Ellul*

Ian C Ellul

## A JOKE A DAY KEEPS THE DOCTOR AWAY

Two hunters are out in the woods when one of them collapses. He doesn't seem to be breathing and his eyes are glazed. The other guy whips out his phone and calls the emergency services. He gasps, "My friend is dead! What can I do?" The operator says "Calm down. I can help. First, let's make sure he's dead." There is a silence, then a gunshot is heard. Back on the phone, the guy says "OK, now what?"

Gurpal Gosal (Manchester)



My husband asked me to dress up as a nurse tonight to fulfill his fantasy... that we have health insurance

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## CALYPSO HOTEL COMPETITION WINNER

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## CONTINUING EDUCATION

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**Dr Alfred Grech MD** graduated from the University of Malta in 1985. He has been working in Primary Health (specifically at Paola Health Centre) for these last 24 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees. The co-author of the article is Dr Sandra Baldacchino.



**Dr Charmaine Gauci MD MSc Dip(Fit&Nut) PhD FRSPH FFFPH** is the director of the Health Promotion and Disease Prevention Directorate. She is a senior lecturer with the UOM and delivers lectures in the field of public health with special interest in epidemiology and communicable diseases. She is active in the field of public health and is currently also president of the Malta Association of Public Health Medicine.



**Daphne Coleiro B.Sc Pharm Science (Hons)** is a final year M. Pharm student. The research carried out under the supervision of Professor A. Serracino-Inglott and Professor L. Azzopardi focused on the financial and environmental impact of storing medicinal products in the community pharmacy.



**Massimo Azzopardi** is an independent catering consultant and event specialist with over 20 years experience in delivering successful events, quality catering and bespoke services designed to reach and exceed guest expectations.



**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 Hospital, Malta.

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**COVER:**  
**'Rite of passage' Oil on canvas 120 x 74 cm**

Professor Simon Attard Montalto was born in 1961, graduated in medicine from the University of Liverpool in 1985 and subsequently specialised in Paediatrics. He forms part of the group so-called 'Painting Paediatricians' and, from an artistic perspective, is entirely self-taught.

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# PRIMA: Health is Wealth

For decades the development of pharmaceuticals has been regulated by safety, efficacy and quality rules for product registration. In public health care systems, these three 'hurdles' are increasingly being supplemented by a fourth: pharmacoeconomics. With the current upheaval of Europe's economy, the financial aspect is playing one of the major roles in healthcare accessibility. *"Health systems are not, as so often portrayed, a drag on resources, but rather part and parcel of improving health and achieving better economic growth. The relationship between health systems, health and wealth is complex but the three are inextricably linked and investing cost-effectively in health systems can therefore contribute to the ultimate goal of societal well-being. Health systems, to the extent that they produce health, could be seen to be a productive sector rather than a drain on our economies, which would in turn force a re-examination of concerns about financial sustainability. Increased spending on effective health systems could be recast as a contribution to a bigger (and more productive) economy, as well as a way of achieving health improvement and higher levels of wellbeing, which themselves are societal objectives."*<sup>1</sup>

European healthcare is a duty, imbedded in our culture, to help people in sickness, to promote a healthy society through education and the prevention of diseases. Human life is our highest value; the concept of health is fundamental to life and

leads to the creation of wealth. Being physically and mentally healthy is of prime importance in life. Being ill or not feeling well can drastically affect your work. Obviously, if you feel physically and mentally healthy, you can be more productive and you can enjoy your life.

Unfortunately due to the current economic scenario, since health is often seen as a cost rather than an investment, cost containment has become a major priority in most health systems. This is a dangerous approach to health that will have repercussions in the near future. Many studies have shown that health is directly proportional to wealth. Significant economic benefits can be achieved by improving health. It was shown that health increases productivity, keeps people active, boosts life expectancy and reduces absenteeism. Healthy citizens contribute to society, form a productive workforce and require less health care, both acute and long term. It is very important to eliminate health inequalities and ensure that even the most vulnerable members of society are not denied their right to good health and healthcare.

## The limiting factor for a society and economy to be healthy is the health of its members.

### References

1. Josep Figueras et al. WHO European Ministerial Conference on Health Systems. Health systems, health and wealth: Assessing the case for investing in health systems; 2008 Jun 25-27; Tallinn, Estonia. p.1
2. "The pharmaceutical industry in figures". EFPIA (European Federation of Pharmaceutical Industries and Associations) Key Data 2012. p.4.
3. "The pharmaceutical industry in figures". EFPIA (European Federation of Pharmaceutical Industries and Associations) Key Data 2012. p.25.

*"The research-based pharmaceutical industry can play a critical role in restoring Europe to growth. In 2011 it invested an estimated €27,500 million in R&D in Europe. It directly employs 660,000 people and generates three to four times more employment indirectly – upstream and downstream – than it does directly. However, the sector faces real challenges. Besides the additional regulatory hurdles and escalating R&D costs, the sector has been severely hit by the impact of fiscal austerity measures introduced by governments across much of Europe in 2010 and in 2011."*<sup>2</sup>

*"Medicines only constitute a small part of disease costs with, on average, 16.7% of total health expenditure in Europe being spent on pharmaceuticals and other medical non-durables. In costly diseases such as cancer and rheumatoid arthritis, medicines account for even less than 10% of the total disease costs. Medicines can also generate additional savings, for example by substantially reducing costs in other branches of healthcare (hospital stays, invalidity, etc)."*<sup>3</sup>

Investment in health cannot be seen only as a cost, but also as a contributor to long term economic growth. The strategic direction of improving human capital makes health central to Europe's development and sustainability: only a healthy population can bring about improved productivity and subsequent increase in GDP, and by doing so ensure economic growth. Hence the old adage "a healthy population is a wealthy population".

### PRIMA

The Public Relations Officer for PRIMA is Nicholas Falzon and he can be contacted on 99822169 or niki@associateddrug.com. The mailing address for PRIMA is P.O. Box 34, Naxxar. 

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No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Asthma: Onbrez Breezhaler should not be used in asthma. Paradoxical bronchospasm: If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. Deterioration of disease: Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Systemic effects: Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. Cardiovascular effects: Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes, in case such effects occur, treatment may need to be discontinued. Hypokalaemia: Beta<sub>2</sub>-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. Hyperglycaemia: Inhalation of high doses of beta<sub>2</sub>-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1.2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. Pregnancy and Lactation: No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. **INTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, headache, cough, rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007 Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 124, Valletta, VLT 1000 Malta. Tel: +356 22983217/+3562 1222872 - 2012-MT-ONB-02-Aug-2012

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1. Cazzola M, Matera M.G. Novel long acting bronchodilators for COPD and asthma. Br J Pharmacol. 2006;155:291-299
2. Novartis European Ltd. Onbrez® Breezhaler® Summary of Product Characteristics.

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# HERVs, Transposons and Human Diseases – Part II

ALFRED GRECH  
SANDRA BALDACCHINO

## The Host Cellular Response to Transposable Elements

It is obvious that TEs can have a neutral, good or bad effect on the genome when they transpose. In the short term TEs can cause havoc when unleashed. The host response to limit the harmful effects of TEs is a multi-layered one directed at the various stages of the life cycle of TEs.<sup>1</sup> Table 7 below hints at some of the known processes that the mammalian cell has developed to repress TE activity. Many of the processes ‘cross talk’ with each other and form complicated networks involving several stages and molecules. It is not the intention of this paper to go into these in detail but the main molecular protagonists are mentioned in the table, for those keen to find out more about the subject.

**Epigenetic modifications** simply refer to chemical tags that are made to the chromatin template rendering it condensed and so repressive for transcription. Specifically, such epigenetic modifications include (i) DNA-methylation and (ii) modifications to tails of histone proteins. Here, some in depth description of these processes is important in order to understand how by knowing them, prevention and

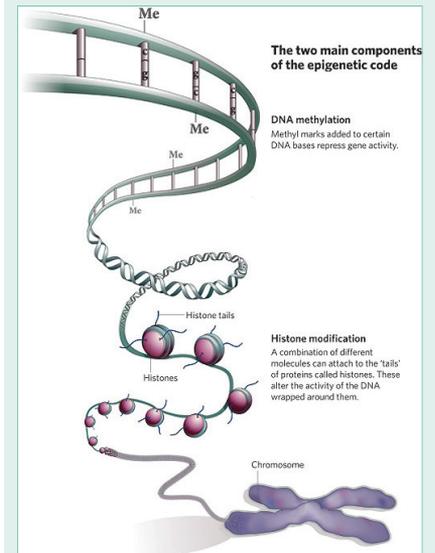
treatment could be devised for some of the medical conditions in which TEs are being implicated in their pathogenesis.

In DNA-methylation, a methyl donor molecule called S-adenosylmethionine donates a methyl group which is covalently added to the carbon-5 position of cytosine within the CpG dinucleotide in the DNA molecule. This reaction is enzyme mediated and is performed by a family of enzymes called **DNA methyltransferases (DNMTs)**.

Histone proteins come together in octamers i.e. 8 molecules, to form the core of nucleosomes around which the DNA double helix wraps. In doing so, they present tails that stick out. These histone tails have amino acids, like lysine and arginine, which can be chemically modified. These chemical modifications of these amino acids on the histone tails affect how the histone proteins interact with DNA, modifying the chromatin template structure and thus act as an epigenetic mechanism.

**Histone acetylation** is one of the best-studied histone modifications. **Histone acetyltransferases (HATs)** catalyses this acetylation and uses acetyl-coenzyme A as a donor molecule. Histone acetylation occurs

**Figure 2:** DNA Methylation and Histone Modification are the two main epigenetic modifications in mammals, including humans (Dr Mark Hill, Molecular Development – Epigenetics (2010))



largely at lysine residues of the histone H4 and H3, which are core histones of nucleosomes. The level of histone acetylation depends on a balance between the action of HATs and **histone deacetylases (HDACs)**. Another histone modification is that of **histone methylation**. Histone methylation is harnessed by a family of enzymes called **histone methyltransferases (HMTs)**. On the other hand and to balance the effect of HMTs when needed, **histone demethylases (HDMs)** remove methyl groups from histone.

Besides these chemical modifications, other proteins are involved, but all may concur to the **heterochromatization** (condensation of chromatin template) of TEs promoters and hence suppress TE expression.

In **RNA editing** the protein coding sequences of mRNAs are modified without involving splicing.

**RNA interference (RNAi)** involves several related processes whereby short RNAs (usually 20-30 nucleotides

**Table 7:** The Multilayered Host Response to TEs

TE Life Cycle Stage	Main Processes Involved	Molecules Involved
1) TE Transcription	Epigenetic modifications	DNA methylation; histone modifications; proteins that bring about the formation of repressive chromatin states
2) Post-Transcriptional Processing of TE RNAs	(i) RNA Editing (ii) RNAi	(i) RNA editases (ADAR family; APOBEC proteins; Dicer protein; Argonaute proteins; short interfering RNA, microRNA, RNA-induced silencing complex, Piwi-interacting RNA)
3) Integration of TE Copies	DNA Repair	DNA repair enzymes e.g. ERCC1/XPF endonuclease

**Table 8:** The Outcome of RNAi

1. Cleavage and degradation of targeted RNA
2. Recruiting additional factors that help modify gene expression
3. Epigenetic modification and heterochromatization

**Table 9:** Some Definitions to Understand Modulation of Gene Expression of Some TEs

<b>Promoter</b>	DNA sequence of a gene to which RNA polymerase binds to start transcription.
<b>Enhancer</b>	DNA sequence that has a transcriptional regulatory function; it can be located at a site remote from the promoter.
<b>Alternative splicing</b>	is the generation of diverse mRNAs by varying the pattern of pre-mRNA splicing.
<b>RNA editing</b>	RNA processing events that alter the protein coding sequences of mRNAs; it does not involve splicing.
<b>Polyadenylation</b>	is the process of adding a poly-A tail to a pre-mRNA. It signals the end of transcription. Most mRNAs in eukaryotes are polyadenylated, and the poly-A tails regulate both translation and mRNA stability. <sup>13</sup>

long) target unwanted nucleic acids, like those of viruses invading the cell or those of transposable elements. Indeed, mounting evidence is showing that RNAi is one of the primary defenses that the cell has against viruses and TEs.<sup>2-5</sup> In the case of TEs, RNAi targets TE transcripts by cleaving them and then degrading them or else prevents TEs transcription by helping

in bringing heterochromatization of their sequence inside the host genome (Table 8).

Some TEs, like non-LTR retrotransposons that cause insertional mutagenesis, can bring about complex chromosomal re-arrangements characterized by  $\gamma$ -H2AX foci on the chromosome. This focus marks where the DNA double-strand breaks

to allow the insertion of the TE sequence. Host DNA repair proteins come into action, when they recognize such induced lesions in the DNA and make appropriate repairs. The **ERCC1/XPF** is one such **DNA repair protein complex**.<sup>6</sup> It is a heterodimer, meaning that it is a molecule with two different subunits. Specifically and functionally, ERCC1/XPF heterodimer has endonuclease properties which help against TE movement during the integration of their life cycle.

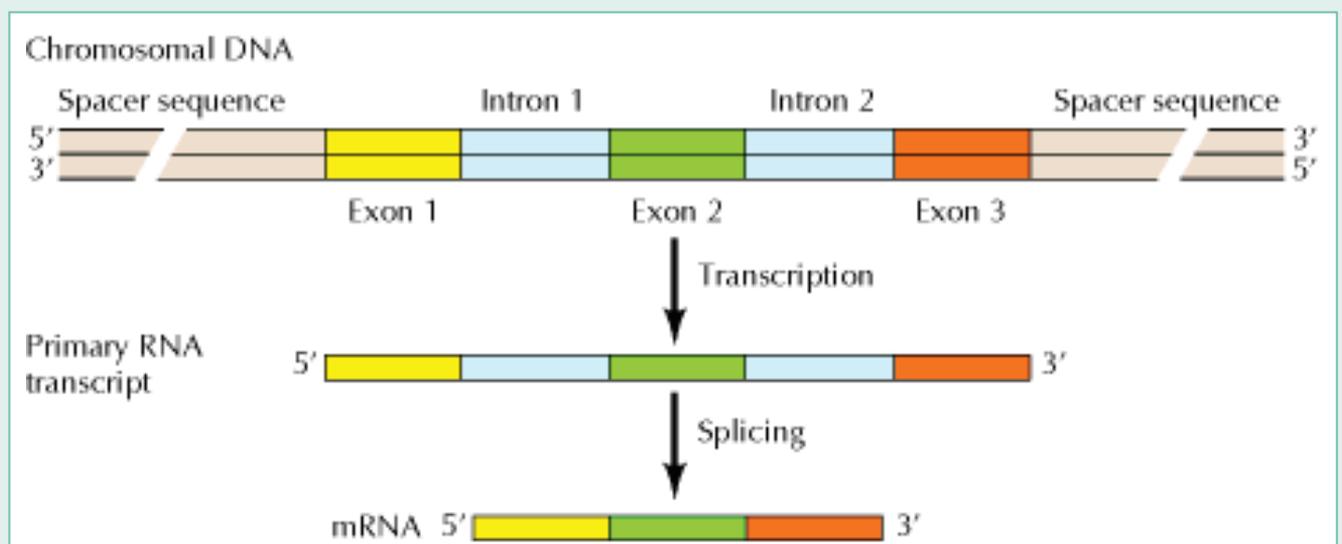
Stopping cell division from occurring is also conducive to suppression of retrotransposition.<sup>7</sup>

Many of the above processes marshalled by the cell to regulate TEs co-evolved as a defence against TEs and have occurred millions of years ago.<sup>8</sup>

*Implicated Physiological/Biological Functions of TE (Including HERVs)*

The biological relevance of TE is starting to be understood. As regards HERVs, most of them in the genome have no effect<sup>9</sup> because their DNA sequence has been disrupted with 'frame-shift mutations', deletions and/or other re-arrangements that render them defective in their three most essential genes (viz. *gag*, *pol*, *env* genes). However, some HERVs could have physiological/biological functions, especially those whose DNA sequence give rise to expressed transcripts and proteins.

**Figure 3:** The Structure of Eukaryotic Genes<sup>15</sup>



### (i) . Evolution of the host

Evolution works on genetic variation. If the environment changes this creates a selection pressure on a population. Under such circumstances, in evolutionary theory, it is envisaged that only those individuals in a population with the right genetic make-up could adapt because of their genetic diversity, and hence will survive (thus the saying 'adapt or perish'). TEs including HERVs could have given rise to countless genetic variations<sup>10</sup> and this could have helped in the evolution of various species, including our own.

So here one sees a situation where the host gets an advantage from the endogenisation (integration inside the genome) of viral sequences. The opposite situation, that is, that where a virus acquires genes from its hosts is also feasible and indeed, many mammalian viruses have done so during their evolutionary pathway.

### (ii). Mammalian reproduction vis-à-vis placental morphogenesis

Sha Mi et al.<sup>11</sup> have shown that HERV-W transcribes a gene (specifically its *env* gene) that encodes a protein called **syncytin**. The expression of this gene occurs mostly in placental syncytiotrophoblasts. Sha Mi et al. also showed that the expression of syncytin in other cells leads to the fusion of cells forming giant syncytia. Their research work clearly shows that HERV-W is thus important in the generation of the human placenta.

### (iii). Acquired immunity in vertebrates

A fusion protein is formed when two or more genes are joined together. Antibodies are such fusion proteins which are produced by the process of **VDJ recombination**. The latter is a complex process that involves cleaving and rearranging DNA sequences that code for the antigen receptors of immunoglobulins. The DNA rearrangements result in various combinations that contribute to a wide diversity of possible antibodies, which can even range into thousands. It is believed that this VDJ machinery evolved from transposons (the **transposon hypothesis of VDJ recombination**).<sup>12</sup> **RAG1** and **RAG2**

**Table 10:** Cases where HERV LTRs contribute to Gene Expression

HERV family	Gene involved	Function
HERV-E <sup>18</sup>	Human apolipoprotein ( <i>APOC1</i> ) gene	Lipid metabolism
HERV-E <sup>19</sup> (alternative promoter)	Human endothelin B receptor ( <i>EDNRB</i> ) gene (on chromosome 13)	The gene codes for the endothelin receptor type B (a 7-transmembrane receptor that mediates the vasoconstrictor actions of endothelins)
HERV-L <sup>20</sup>	Human beta 1,3-galactosyltransferase	in type 1 Lewis antigen synthesis GIT and mammary gland
HERV-H <sup>21</sup>	HHLA2 and HHLA3	immuno-protection in intestinal tissues, kidney, and lung

(for **recombination-activating genes**) are two essential genes for VDJ recombination and it is proposed that the DNA now coding RAG1 and RAG2 was once a mobile element.

### (iv). Modulation of gene expression

Some definitions (Table 9) are appropriate here in order to understand the roles played by some TEs in modulating gene expression.

Genes have a split structure in which segments of coding sequence (called **exons**) are separated by noncoding sequences (intervening sequences, or **introns**). When a gene is transcribed a **pre-mRNA** (also called **primary RNA transcript**) is produced. In a process called **splicing**, introns are removed and the exons are joined together, and a **mature mRNA** is formed. Splicing leads to the synthesis of different homologs from the same primary RNA transcript, since exons of the latter can be shuffled around before being joined together. Homologs imply molecules that have the same origin but differ in function.<sup>14</sup>

**Exaptation** is the process whereby relics of TEs acquire a regulatory function. For example, **HERVs have their own transcriptional promoters, regulators and enhancers in their Long Terminal Repeats (LTRs)**. Thus these sequences if not disrupted can and do initiate transcription of their *gag*, *pol* and *env* genes, but not only. They also start transcription of neighbouring genes. HERVs can also signal splicing generating diverse transcripts (mRNA) of neighbouring cellular genes. Modulations of genes

have also been demonstrated by *Alu* elements. This occurs at the post-transcriptional level in three ways, (i) RNA editing, (ii) alternative splicing and (iii) translation regulation.<sup>16</sup> Nishihara et al.<sup>17</sup> also showed that a very conserved sequence belonging to a SINE subfamily can act as a **distal cis-regulatory element**. The latter is a DNA sequence regulating the expression of a gene located on the same DNA molecule (hence the *cis* = intra-molecular) but is remote to the gene it affects. Such regulatory elements are often sites where **trans-acting factors** (intermolecular proteins) bind.

### (v). Cell metabolism

Rubin et al.<sup>22</sup> and Liu et al.<sup>23</sup> demonstrated that certain TE transcripts, specifically *Alu* RNAs, show a transient increase in the cytosol under numerous stressful states (e.g. viral infections, heat shock and exposure to cycloheximide). They proposed that these *Alu* RNAs might function in cell metabolism under stressful conditions.

### (vi). Protection against some exogenous retrovirus infections

HERVs have also been shown to confer host cell resistance to some exogenous retroviruses by blocking the exogenous retrovirus replication by either receptor interference or through antisense mRNA.<sup>24</sup> S

(to be continued)

References may be accessed at [www.thesynapse.net](http://www.thesynapse.net)

# Breaking the laxative loop

## Alternative therapeutic option for patients suffering from chronic constipation

Chronic constipation is a widespread, sometimes bothersome disorder that warrants improved recognition and management<sup>1-3</sup>. Chronic constipation is characterised by the infrequent and difficult passage of stools (typically fewer than three bowel movements per week) over a prolonged period of time.<sup>4,5</sup> Additional troublesome symptoms may include excessive straining with defaecation, hard or lumpy stools, sensation of incomplete evacuation after a bowel movement, bloating and abdominal pain or discomfort.<sup>4,5</sup> More commonly experienced by women than men, it is estimated that almost one-fifth of the population in Europe suffer from the condition.<sup>6,7</sup> Many of these patients suffer in silence<sup>5</sup> or remain dissatisfied with the efficacy of traditional therapies,<sup>4,8,9</sup> therefore a need exists for additional therapeutic options.<sup>2</sup> New therapies are becoming available for chronic constipation that may offer effective relief from symptoms, most notably selective gastrointestinal prokinetic agents such as prucalopride (Resolor®; Shire), which is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.<sup>10</sup> A prokinetic agent like Resolor® may help to normalise bowel movements, and, therefore, has been recommended in recent European expert guidance as an alternative treatment option for chronic constipation in women who don't gain adequate symptom relief from traditional therapies.<sup>5</sup>

### Prevalence of chronic constipation

Chronic constipation is a multi-symptom condition characterised by infrequent defaecation, hard or lumpy stools, straining, abdominal bloating and discomfort, and sensation of incomplete evacuation after a bowel movement.<sup>5</sup> Pharmacists may play a role in providing advice and guidance to patients who repeatedly attempt various laxatives to relieve the distress of their condition without success. These patients should be considered for an alternative treatment. Estimates of the prevalence of chronic constipation in Europe range from 5% to 35%, while a global estimate places the prevalence at 14%.<sup>6,7</sup> Women are particularly affected by chronic constipation, with prevalence estimates of 17.4% versus 9.2% in men. Thus, women are twice as likely as men to be affected by the condition.<sup>7</sup>

### Impact of chronic constipation

For a proportion of patients, constipation can be a chronic and sometimes severe and bothersome disorder.<sup>4,5</sup> In a US survey that explored the frequency and duration of chronic constipation symptoms, 557 adult patients (44% men, 56% women) reported experiencing symptoms, on average, 3.2 days per week for 4.2 years and, in 21%, the duration of symptoms was at least 10 years.<sup>4</sup> Severity of chronic constipation was rated by more than half (54%) of patients in this survey as "extremely", "very" or "somewhat" severe and most (76%) rated their constipation as "extremely", "very" or "somewhat" bothersome.<sup>4</sup> Bloating, straining and hard stools were considered by patients to be the three most bothersome symptoms. Symptoms were more bothersome among patients with a long duration of illness (6 years or more). Quality of life may be negatively affected by chronic constipation, with 52% of patients in the US survey indicating the condition affects their quality of life "somewhat", "a lot" or "a great deal". Social or personal impairment was also reported by a substantial proportion of patients (73%) as a result of symptoms.<sup>4</sup> Societal burden of chronic constipation is exemplified by the higher rate of absenteeism from work that ensues in affected patients.<sup>4,11</sup>

### Breaking the laxative cycle

Breaking the cycle of repeated laxative failure may prevent patients continuing to self-medicate unsuccessfully with multiple medication trials. Unfortunately, many patients with chronic constipation suffer in silence and attempt to self-medicate without seeking professional help.<sup>5</sup> Of those who do seek advice from a healthcare professional and receive a pharmacological treatment, only 27% are satisfied with the available therapies according to a European survey of 744 patients,<sup>8,9</sup> while the US survey indicates that lack of efficacy and safety concerns are key reasons for treatment dissatisfaction.<sup>4</sup> Constipation can arise from a range of primary (idiopathic) causes, or occur secondary to various lifestyle factors and medical conditions or even medications.<sup>13,14</sup>

Recent European expert guidance on the treatment of chronic constipation recommended that, where diet, lifestyle measures and traditional laxative therapies fail to provide adequate relief for female patients, laxative therapy should be stopped and treatment with a prokinetic motility agent, such as Resolor®, started (Figure 2).<sup>5,10</sup>

### Prokinetic motility agent: an alternative mechanism of action for chronic constipation

Resolor® is a gastrointestinal prokinetic agent – a selective, high-affinity 5-HT<sub>4</sub> receptor agonist – that is pharmacologically distinct from traditional therapies.<sup>10</sup>

Pooled data from three large, randomised, double-blind, placebo-controlled, 12-week studies showed that one in four adult female patients with chronic constipation experienced normalisation of bowel function with Resolor® 2 mg once daily. The same pooled data showed that Resolor® 2 mg resulted in significant improvements in a validated and disease-specific set of symptom measures (the Patient Assessment of Constipation-Symptoms questionnaire), including abdominal, stool and rectal symptoms, determined at Weeks 4 and 12.<sup>10</sup>

### Administration of Resolor®

Resolor® is a prescription medicine that is easy to use and should be taken taken as 2 mg once a day, every day, at any time (with or without food).<sup>10</sup> Dose adjustments are required for elderly patients (>65 years), who should start on 1 mg once daily and increase to 2 mg if required; for patients with severe renal impairment, who should be treated with 1 mg once daily; and for patients with severe hepatic impairment, who should start with 1 mg once daily then increase to 2 mg if required to improve efficacy and if the 1 mg dose is well tolerated.<sup>10</sup> An image of the Resolor® package that will be dispensed is shown in Figure 1. Resolor® has a low potential for drug-to-drug interactions.<sup>10</sup> Resolor® is not recommended in men, children and adolescents <18 years.<sup>10</sup>

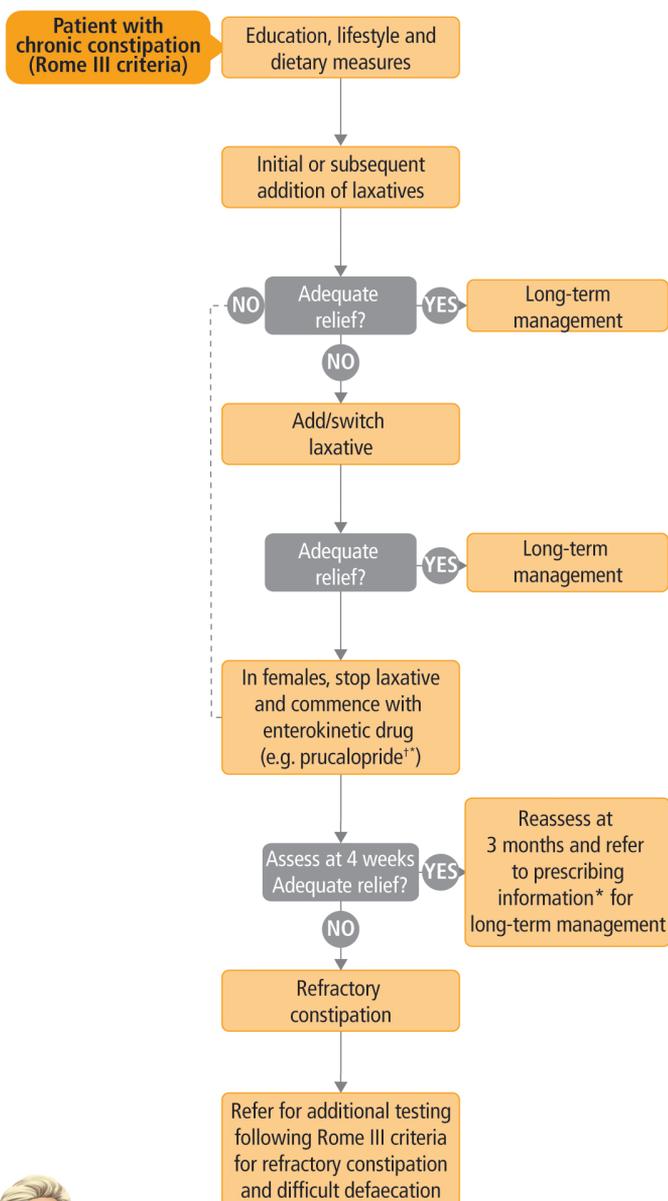
Pharmacists may play an important role in patient education and support around the dosing regimen.<sup>10</sup> Such pharmacy-led education should aid patient adherence with treatment.<sup>15</sup>

Figure 1. Image of Resolor® pack for dispensing



**Figure 2. Recommendations for a treatment algorithm for chronic constipation developed by European experts in 2011.**

Extract from full algorithm – for full version, please refer to reference.<sup>5</sup> Adapted with permission from Tack *et al. Neurogastroenterol Motil* 2011. <sup>1</sup>2 mg Resolor<sup>®</sup> per day (or 1 mg per day in patients aged >65 years).



\*Please refer to full prescribing information for Resolor<sup>®</sup>.

## Prescribing Information

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

### RESOLOR<sup>®</sup> (prucalopride)

Selective serotonin (5-HT<sub>4</sub>) receptor agonist, enterokinetic agent, available as 1 mg and 2 mg film-coated tablets for oral administration, once daily, with or without food, at any time of the day.

**Indication:** Resolor<sup>®</sup> is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. **Dose:** Women: 2 mg once daily, elderly (>65 years): Start with 1 mg once daily and increase to 2 mg once daily if necessary. Patients with severe renal impairment (GFR <30 ml/min/1.73 m<sup>2</sup>): 1 mg once daily. Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2 mg if required to improve efficacy and if the 1 mg dose is well tolerated. No dose adjustment required in patients with mild to moderate renal or hepatic impairment. Men, children and adolescents <18 years: not recommended until further data become available. **Contraindications:** Hypersensitivity to prucalopride or any of the excipients. Renal impairment requiring dialysis. Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, and ulcerative colitis and toxic megacolon/megarectum. **Precautions:** Caution should be exercised when prescribing Resolor<sup>®</sup> to patients with severe hepatic impairment (Child-Pugh class C) due to limited data in patients with severe hepatic impairment. Patients with severe and clinically unstable concomitant disease (e.g. cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) have not been studied. Caution should be exercised when prescribing Resolor<sup>®</sup> to patients with these conditions. In particular Resolor<sup>®</sup> should be used with caution in patients with a history of arrhythmias or ischaemic cardiovascular disease. In case of severe diarrhoea the efficacy of oral contraceptives may be reduced and an additional contraceptive method is recommended. Contains lactose monohydrate. Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not take Resolor<sup>®</sup>. **Interactions:** Prucalopride has a low pharmacokinetic interaction potential. Studies in healthy subjects did not show a clinically relevant effect of prucalopride on the pharmacokinetics of warfarin, digoxin, alcohol, paroxetine or oral contraceptives. A 30% increase in plasma concentrations of erythromycin was found during prucalopride co-administration. The mechanism for this interaction was not clear. Ketoconazole increased the systemic exposure to prucalopride by 40%. This effect is too small to be clinically relevant. Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride. **Pregnancy:** Animal studies did not indicate harm. Experience of Resolor<sup>®</sup> during human pregnancy is limited. Cases of spontaneous abortion have been observed in human clinical studies although, in the presence of other risk factors, the relationship to Resolor<sup>®</sup> is unknown. Resolor<sup>®</sup> is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with Resolor<sup>®</sup>. **Lactation:** Prucalopride is excreted in breast milk, however at therapeutic doses no effects are anticipated on the breastfed newborn/infant. In the absence of human data Resolor<sup>®</sup> is not recommended during breastfeeding. **Effects on ability to drive and use machines:** No studies have been performed. Resolor<sup>®</sup> has been associated with dizziness and fatigue, particularly on the first day of treatment, which may affect driving or using machines. **Side effects:** The most commonly reported side effects in Resolor<sup>®</sup> clinical trials were headache and gastrointestinal symptoms (abdominal pain, nausea, diarrhoea) occurring in about 20% of patients each. These events occur mostly at the start of therapy and usually disappear within a few days whilst continuing Resolor<sup>®</sup>. Other common adverse events in controlled trials included dizziness, vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds, pollakiuria and fatigue. Uncommon adverse events included anorexia, tremors, palpitations, fever and malaise. After the first day of treatment the most common adverse events were reported with similar frequency for Resolor<sup>®</sup> and placebo except nausea and diarrhoea: these remained higher but the difference between Resolor<sup>®</sup> and placebo was smaller (1 to 3%). Palpitations were reported in 0.7% of placebo patients, 1.0% of 1 mg Resolor<sup>®</sup> patients and 0.7% of 2 mg Resolor<sup>®</sup> patients. As with any new symptom, patients are advised to discuss new onset palpitations with their physician. **Pack size:** 28 tablets (4 blisters with 7 tablets) EU/1/09/581/001 (1 mg), EU/1/09/581/002 (2 mg). **Legal category:** POM. **Marketing Authorisation Holder:** Shire-Movetis N.V., Veedijk 58 (1004), 2300 Turnhout, Belgium. **Date of preparation:** March 2012.

Adverse Events should be reported to Vivian Corporation on  
Tel: 21344610/21344616/21320338  
Email: pv@viviancorp.com

## Safety information

Please consult the Resolor<sup>®</sup> Prescribing Information before prescribing, particularly in relation to hypersensitivity to any of the constituents, renal impairment requiring dialysis, intestinal perforation or obstruction, obstructive ileus, severe inflammatory conditions of the intestinal tract, severe and clinically unstable concomitant diseases, in particular arrhythmias or ischaemic cardiovascular disease.

Very common side effects associated with Resolor<sup>®</sup> are headache, nausea, diarrhoea and abdominal pain, occurring predominantly at the start of therapy and usually disappearing within a few days with continued treatment. Common side effects are dizziness, vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds, pollakiuria and fatigue.

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 **Resolor<sup>®</sup>**  
prucalopride  
Time to move forward

 **Shire**

To be as brave as the people we help.

# Storing medicines while reducing electricity consumption

## Abstract

Temperature storage requirements for medicinal products stored at room temperature were compiled. The rate of heat loss in a local pharmacy was investigated. Necessary measures required to achieve temperature controlled storage conditions in the most efficient manner were proposed. Energy efficiency together with carbon emission reductions were calculated.

## Introduction

Pharmaceuticals should be stored under conditions recommended by the manufacturing company at all times to prevent deterioration of the product.<sup>1</sup> Proper storage ensures that medications are safe for their intended use, without losing their efficacy or causing undue adverse drug reactions.<sup>2</sup> The impact of exposure of medicinal products to temperatures which are outside room temperature (maximum of 25°C) is not well documented. Maintaining a community pharmacy or a pharmaceutical store at 25°C in the local scenario, where during summer months the temperature is normally above 30°C, requires a large investment in temperature control mechanisms and an indirect environmental impact. Yet, little is known about the impact on specific products if they are stored at higher temperatures than 25°C limit.

Temperature variations between 15°C to 30°C may be experienced in pharmaceutical storage areas. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted only if the manufacturer instructs so.<sup>3</sup> Stability studies show that in periods of heat waves, drugs do not deteriorate unless the heat wave exceeds the period of 6 months. This is because the temperature is not constantly 40°C.<sup>3</sup> Also the temperature reaching the core of the drug remains much lower than

the ambient temperature due to the limitation of heat exchange provided by packaging material.<sup>4</sup>

## Method

Storage conditions were compiled for the medications listed in the Marketing Authorisation.<sup>5</sup> Information regarding the recommended storage conditions of these products was gathered from published research papers,<sup>5,6</sup> the respective Summary of Product Characteristics and the Patient Information Leaflet. When this information was not available, the manufacturing company was directly contacted for each particular product

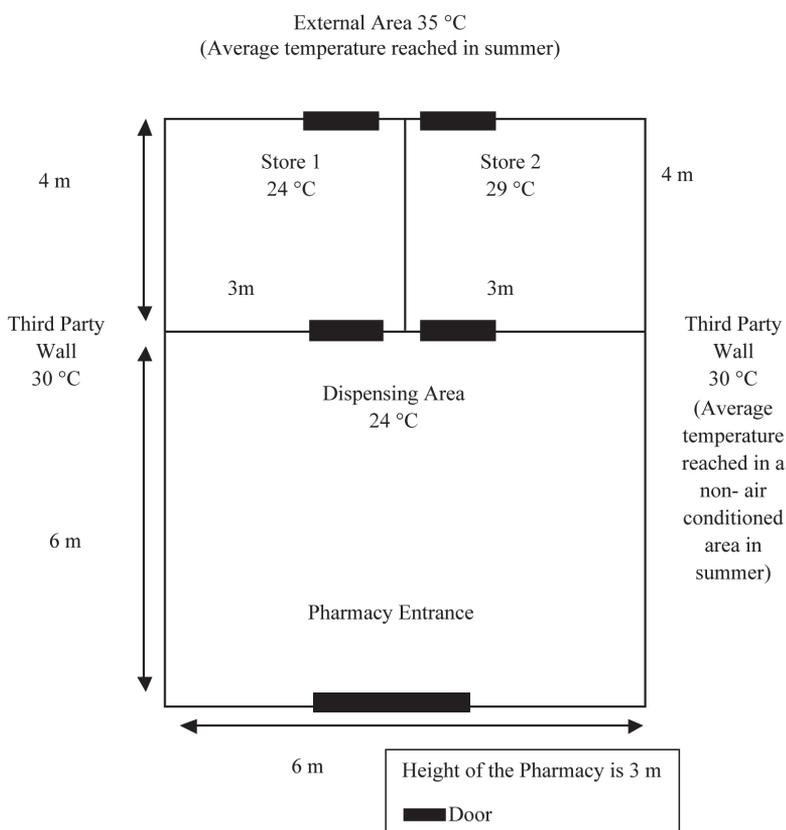
and was asked to provide storage data specific for the Maltese climate zone.

## Results and Discussion

Data was collected for 1794 medications after reviewing SmPC and directly from manufacturing companies. It resulted that 1039 medications should be stored below 25°C, 414 below 30°, 4 medications below 37°C and 334 have no special temperature storage conditions. Three medications should not be exposed to temperatures above 50°C, due to the presence of pressurised gas.

The rate of heat loss in a typical Maltese pharmacy was investigated. A pharmacy plan was laid out, depicting

Figure 1. Pharmacy Plan



A plan of a typical pharmacy was set so that the heat losses could be calculated. This is a 60m<sup>2</sup> pharmacy consisting of a main dispensing area having an area of 36m<sup>2</sup> and 2 stores (12 m<sup>2</sup> each). Both stores have access to an external area. It is assumed that on either side of the pharmacy there are third party buildings. Each area is equipped with an efficient air conditioner; assumed to be 32.5% efficient.<sup>7</sup>



Temperature variations between 15°C to 30°C may be experienced in pharmaceutical storage areas

a 60m<sup>2</sup> pharmacy area, consisting of a main dispensing area and two stores linked to the dispensing area through a door (Figure 1). Medicines are grouped according to the maximum temperature storage conditions permitted in the two different isolated stores of the pharmacy.

For efficient temperature control, an integrated air conditioned system could be installed which ensures that designated areas have the specific recommended temperature conditions namely less than 25°C and 30°C respectively, reflecting a substantial reduction in cooling capacity.

It is possible to store 1039 different medicinal products (stable below 25°C) in store 1 and in the dispensing area. The remaining 755 medications (stored below 30°C or have no special temperature storage conditions) are stored separately in store 2. The air conditioning temperatures should be set to 24°C and 29°C respectively, ensuring that all medications are stored in accordance to their storage requirements.

Heat losses could be further minimized by installing doors between Store 2 (29°C) and the dispensing area (24°C). In general for all sections of a pharmacy, reduction in cooling capacity can be achieved by reducing heat losses, using UV blocking double glazed doors leading to external areas of the pharmacy and air curtains at the main entrance if doors are frequently left open. Future considerations include roof, floor and wall insulation coatings and the use of photovoltaic solar panels.

In a smart pharmacoeconomic scenario of segregation of medications according to maximal tolerated temperatures being a cardinal turning point for a reduction in required cooling capacity, electrical efficiency and reduction in carbon dioxide emissions were calculated. For one pharmacy, over €580 and over 3150kg of CO<sub>2</sub> can be saved during the summer months (May to September) when high temperatures are reached. These figures were worked out on the current electricity cost in Malta, where 1 kWh

costs €0.161 and produces 0.871 kg of CO<sub>2</sub>. Taking into consideration all the 215 pharmacies in the Maltese islands, a total of €124,700 can be saved, and around 677,250kg of CO<sub>2</sub> avoided every summer. <sup>8</sup>

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# GALVUS and EUCREAS COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

## INSULIN INCREASE

## GLUCAGONEDOWN NEW

**GALVUS® is indicated as a triple oral therapy in combination with an SU and metformin<sup>1</sup>**  
**EUCREAS® is indicated as triple oral therapy in combination with an SU<sup>2</sup>**  
**GALVUS® and EUCREAS® indicated for use in conjunction with insulin<sup>1,2</sup>**

**GALVUS** is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement<sup>1</sup>  
**EUCREAS** is the combination of a DPP-4 inhibitor, GALVUS, and metformin<sup>2</sup>

### Galvus® 50mg (vildagliptin) tablets

**PRESENTATION:** Each tablet contains 50 mg of vildagliptin. **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults. As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin, a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance, a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSEAGE:** When used as monotherapy in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents less than 18 years old due to lack of data on safety and efficacy. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years). The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients. Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose maldigestion should not take this medicine. Galvus should not be administered during pregnancy or lactation since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, gliclazide, metformin), amiodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). **Metformin monotherapy:** Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. **Combination with metformin:** Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. **Combination with sulphonylurea:** Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. **Combination with Thiazolidinedione:** Common: weight increase, oedema peripheral. Uncommon: headache, asthenia, hypoglycaemia. **Combination with insulin:** Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea, flatulence, frequency, not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bulous or exfoliative skin lesions. **LEGAL CATEGORY:** POM. **PACK SIZES:** 7, 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimborneur Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 002. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 124, Valletta, VT 1000, Malta. Tel: +356 22983217. 2012-MT-GAL-005-Nov-2012.

### Eucreas® (vildagliptin/metformin hydrochloride) film-coated tablets

**PRESENTATION:** Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSEAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy. The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled at dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function (e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents). Acute or chronic disease which may cause tissue hypoxia (e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation). **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III IV and therefore use is not recommended in these patients. Metformin is contraindicated in patients with heart failure, therefore Eucreas is contraindicated in this population. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not restarted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, gliclazide, metformin), amiodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances (e.g. cimetidine and intravascular administration of iodinated contrast media). Combinations requiring caution include metformin hydrochloride with medicines tending to prolong the hypoglycaemic effect of metformin (e.g. sulphonylureas, beta agonists and diuretics). The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. **Vildagliptin Monotherapy:** Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. **Metformin monotherapy:** Very common (>1/10): Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. **Combination vildagliptin with metformin:** Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. **Combination with metformin and sulphonylurea:** Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. **Combination with insulin:** Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM. **PACK SIZES:** 30, 60 film-coated tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimborneur Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002-003, EU/1/07/425/003-009. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 124, Valletta VT 1000, Malta. Tel: +356 22983217. 2012-MT-EUC-005-Nov-2012.

# Physical activity and mental well-being

There is increasing research into the relationship between physical activity and mental health. Evidence shows that for adults at least 30 minutes of moderate intensity physical activity on most days of the week can improve mood and decrease anxiety and stress and improved self-perception. Physical activity is also thought to have a role in preventing serious mental illness such as depression.

One definition of mental health is that it is 'a positive sense of wellbeing and of being able to cope with the pressures of life.' Most of us experience changes in our moods from time to time and can have periods where we feel down or situations that make us anxious or stressed. The effects of regular physical activity on mood have mainly been studied using aerobic exercise, but evidence indicates that anaerobic physical activity, such as body building or flexibility training, can also reduce depressive symptoms. In contrast, in literature no consensus exists with respect to anxiety symptoms, with some studies showing that anaerobic activity is as effective as aerobic exercise, while others do not.

Physical activity also has beneficial effects for the prevention and treatment of different diseases, and evidence indicates that this assertion is probably true for psychiatric diseases such as

depressive and anxiety disorders. Nevertheless one needs to remember that physical activity can also be harmful, especially when performed in an inappropriate or in a very intense manner. Some conditions which have been reported have been termed as "excessive exercise" and "overtraining syndrome". These may actually cause deterioration in mood conditions. Results of meta-analysis suggest that moderate regular exercise should be considered as a viable means of treating depression and anxiety and improving mental well-being in the general public. Exercise has also been shown to improve aspects of mental functioning such as planning, short-term memory and decision making.

Physical activity has psychological benefits too. It can:

- improve self-esteem
- give a sense of control on life
- promote a sense of positive achievement
- help with weight management
- provide opportunities for socialising and making new friends.

At least 30 minutes of moderate intensity physical activity on most days of the week is the recommended amount for adults. The World Health Organisation states that this amount does not have to be done all at once. Activity can be built up throughout the day. For example, three short sessions of brisk walking for ten minutes provide equal benefits.

Several differing psychological and physiological mechanisms have been proposed to explain the effect of physical activity on mental health disorders and mental well-being. Physical activity has been shown to be related to release of ACTH and  $\beta$ -endorphin into the blood stream. This may be related to the pleasant 'feel good' factor often felt after being active.

There is a huge range of things a person can do including:

- walking
- jogging
- swimming
- tennis
- dancing
- yoga
- aerobics
- weight training
- playing team sports such as soccer, netball, badminton and touch football.

Day-to-day activities such as household chores, walking the dog, playing with the kids and taking the stairs at work instead of the lift are also good for your health. Any activity that gets a person moving physically, improves strength or extends the range of movement is likely to increase the 'feel good' factor.

Health care professionals are key to promoting physical activity. A controlled trial has shown that a prescription for physical activity from a general practitioner, supplemented by additional written support materials, can lead to modest short-term improvements in self-reported physical activity levels among inactive patients. Hence we encourage all health professionals to promote physical activity for their patients in order to improve their health and well-being. 

Support material is available from the directorate.

Call on 23266000

or email [health.pro@gov.mt](mailto:health.pro@gov.mt)



# From HUMAN to ANIMAL medicine

## JOSEPH JOHN VELLA

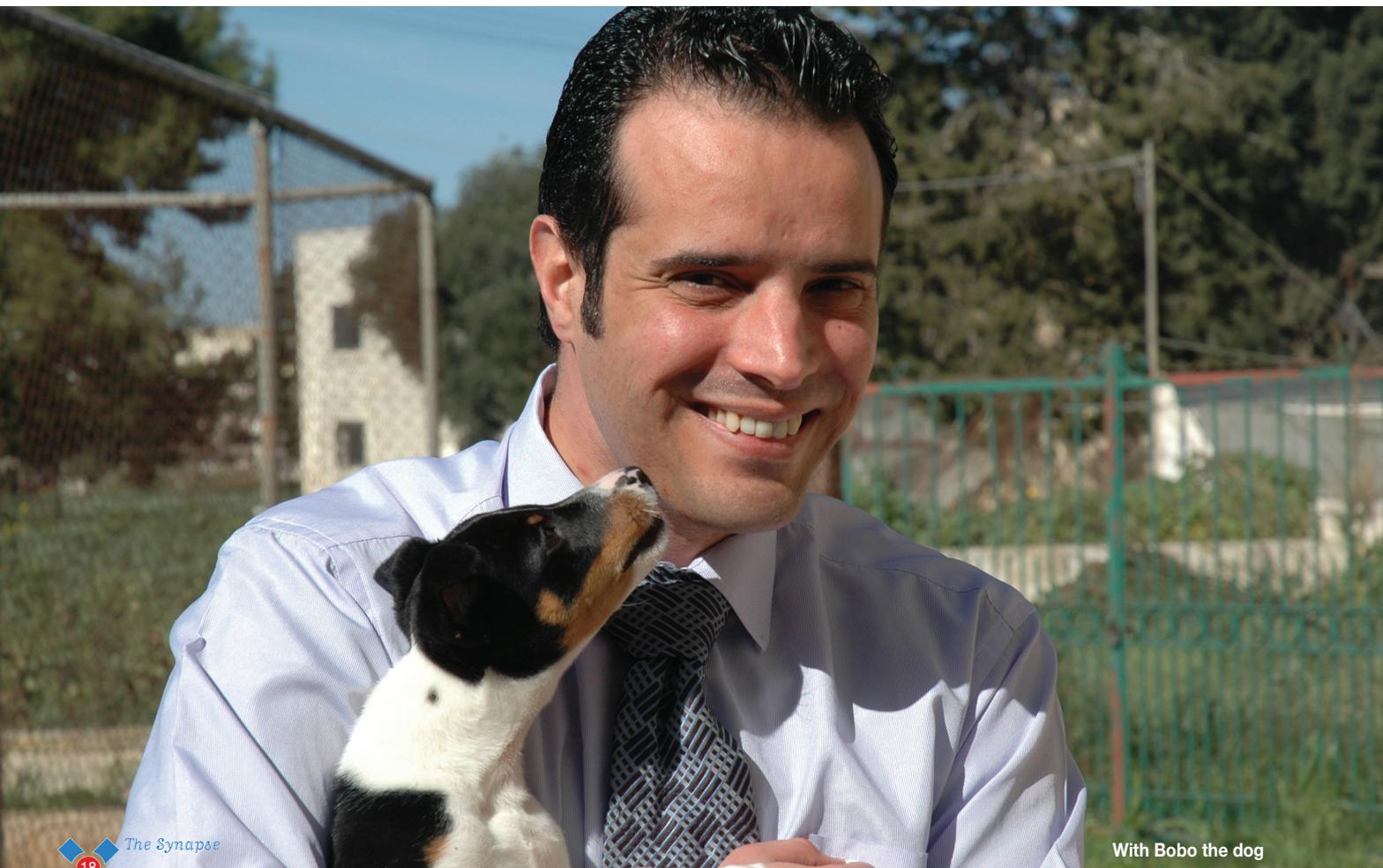
For the past 18 months, the Ghammieri Government Farm has seen a new director overseeing the Animal Welfare, Promotion & Services Directorate which is part of the Veterinary & Phyto-Sanitary Regulation Department. Joseph John Vella is not your typical government department director who has been sitting behind a desk from day one. His story is a dynamic one which started out as a pharmacy student, several years ago.

“I started out studying pharmacy in order to follow up what has been

my life-long passion – molecular genetics. My first research way back in 1995, was in molecular genetics and from then onwards I have kept up my research, albeit on the side, to this day. I am presently researching the regulation of a particular gene, CCR4, in asthma patients. Going back to my student years, I did the usual experiential stint as other pharmacy students do and in my case, worked at the government medical stores, the in-patients’ pharmacy, the out-patients’ dispensary... this for two years

until I decided to veer my studies and concentrate on medicinal plants. Then I proceeded to do a Master of Science in agriculture and veterinary pharmacy.”

His first indirect brush with animal welfare came in 2002 when he worked on medical residues and contaminants in meat at the Government Abattoir in Marsa. From then onwards, he proceeded to hold several posts which brought him into contact with the varied aspects in which animal and plant life interact with humans and their health. He worked at the Plant

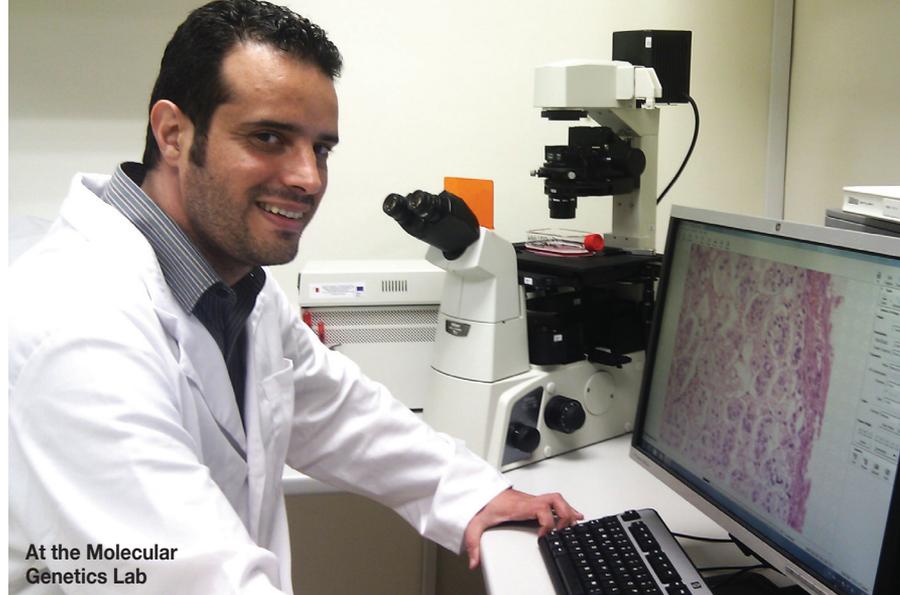


Health Department with responsibilities linked to the control of pesticides, collecting samples and analysing them in order to support legislative moves which needed to be concluded at a pre-EU-accession stage. “The studies that were being carried out at the time contributed to finally seeing several dangerous pesticides being withdrawn from local use, according to EU regulations. It was from there that I moved on to the Animal Nutrition Unit and started a process linked to HACCP (Hazard Analysis & Critical Control Points) guidelines.”

The work included checking feed additives, the withdrawal of growth promoters, the introduction of a ban on certain animal proteins, the analysis of fodder, labelling and more. Joseph John’s work took him on to start contributing to the registration of veterinary medicinals, pesticides and biocides. This saw him also being involved in several standing committees in Malta, the UK and in Brussels. “At a certain point, when things were especially hectic, I had to travel abroad twice a week. The work was intensive but my learning curve was huge and all the experience led me to eventually feel capable of taking on the post of principal, soon after becoming assistant director of veterinary operations.”

Responsibilities in this new role were even more intense and included the control on meat processing plants, border inspections, overseeing of abattoir operations, veterinary laboratory procedures, the twinning project, fisheries, fishing fleet register, and San Luċjan operations within the aquaculture sector ... amongst others. But this 35-year-old pharmacist felt extremely lucky to be touching on so many new sectors that were, finally, all linked and inter-twined in more ways than one.

“It was indeed a constant workload that required attention to detail. However, I am the kind of person who works with huge dedication and passion. Enthusiasm is constant and this, coupled with my great respect for animals and plant life, constantly urged me to do my best at all times. Even when I returned to an administrative role, I took on a work-load that involved



At the Molecular Genetics Lab

HR, capacity building, management of cost centers, and the implementation of new procedures in the Public Administration. It was a time when abattoirs were experiencing the regulator/operator divide and work was particularly intense, requiring great diplomacy. I found myself at the helm of operations that were changing the face of things to come.”

Joseph John’s career proceeded rapidly to an acting director’s post responsible for the civil abattoir, pitkali markets, the fish market, European Fisheries funds and fishing fleet facilities which post lasted for four months. He was eventually accepted for the post of Director of Animal Welfare and even whilst he is still presently overseeing ongoing projects from his last post, such as those linked to the European fisheries fund or the construction of the new fish market in Albert Town, Marsa, he is now fully immersed in the improved national spur towards better animal welfare all round.

“I had applied for the post of director of animal welfare and was accepted immediately. It was yet again a time to move on, always carrying with me this enormous baggage that I never imagined I would carry when I started out researching biochemistry. Animal welfare is a topic many people wrongly believed to be just about caring for stray cats and dogs. That is far from the case. However we also manage the free ambulance service for stray animals, taking strays to the San Frangisk Centre for Stray Animals, giving

them all necessary medical care and eventually possibly re-homing them.”

But animal welfare involves much more than that. The department is working on introducing a more inclusive vision of animal welfare which encompasses farm animals and exotic animals, as well as short distance transport of animals. “All animals should be housed, cared for and fed well. For instance, we check that sows are grouped together, and that slat widths are in line with the legislations. We inspect private homes where abuse may be occurring, as well as pet shops and anywhere exotic animals are kept ... then there are the neutering schemes, as well as the construction of horse shelters and the dog park amongst others. The work involves full collaboration with animal sanctuaries and pro-animal groups, as well as with animal cooperatives.” The fight against animal neglect is a constant even whilst Joseph John admits the entire sector has gone through massive improvements.

Today he feels that much richer for all his experience around the care of animals. “Animals surprise me in more ways than one and one constant fascination is how much animals understand. I am impressed with the amazing bond animals form with their owners, whether animals are guide dogs or simply budgerigars. My own budgerigars are all finger tame, call me by name and know when I am out of the house or in it. Once you become acquainted with the behaviour of animals you cannot stop being amazed by them.” S

# Endometrial Imaging - Part II

In the last article, the changes observed in the appearance of the normal endometrium during the prepubertal, menarchial and reproductive periods were discussed. The current article will present the findings seen in the peri- and postmenopausal endometrium.

A strict determination of menopausal status is difficult, as the process represents a continuum that begins with perimenopause, a time span in which the patient experiences menstrual cycles of variable length and volume of flow, often with skipped cycles. Patients are officially deemed postmenopausal when they have experienced amenorrhea for 12 consecutive months from the date of the last menstrual flow, although sporadic ovulatory cycles have been reported rarely in postmenopausal women.

Although transabdominal US performed with the full bladder technique allows diagnostic imaging in some peri- and postmenopausal women, the modality has limitations. Transabdominal pelvic US may be compromised by a variety of senescent changes, including decreased urinary bladder capacity, increased body habitus, and an atrophic and ill-defined endometrial canal. In many

postmenopausal women, endovaginal US is required to adequately image the endometrium.

The most rapid decline in uterine size occurs within the first 10 years after menopause, with a more gradual decline thereafter. The uterus ranges from 3.5 to 7.5 cm in length and from 1.2 to 3.3 cm in anteroposterior diameter in patients older than 65 years with the wide ranges reflecting variations in patient parity, the number of years since the onset of menopause, and the presence of pre-existent uterine disease such as adenomyosis and myomas.

There is also a decrease in endometrial thickness from the peri- to the postmenopausal periods. The postmenopausal endometrium is typically atrophic because of the lack of estrogen stimulation and appears as a thin hyperechoic line or band measuring only 1–2 mm in maximum diameter (Fig 1). The relatively vascular and compact inner myometrial layer which surrounds the endometrium appears hypoechoic. A small amount of endometrial fluid, less than 2 mm in diameter, may be seen in a postmenopausal patient with an otherwise normal uterus, usually as a result of mild cervical stenosis. This fluid should be excluded from the

endometrial thickness measurement (Fig 2).

The myometrial appearance is often more heterogeneous in postmenopausal women than in premenopausal women, and the uterine body-to-cervix length ratio postmenopause approaches 1:1. Calcified uterine arcuate vessels are commonly noted in elderly postmenopausal women, especially those with diabetes, vascular disease, hypertension, or hypercalcemia (Fig 3). Free peritoneal fluid is occasionally seen in postmenopausal women and is not necessarily pathologic when small in amount and simple in appearance especially in early menopause. Free fluid in late menopause is abnormal and could be related to a variety of conditions, including intraperitoneal malignancy and ascites due to cardiac, renal, and liver disease.

A normal endovaginal sonogram in a postmenopausal patient has a high negative predictive value and high overall accuracy rate for excluding major disorders of the uterus and ovaries, with excellent pathologic correlation. It has been shown that measurements of the endometrium obtained with endovaginal US are within 1 mm of those obtained at pathologic examination and



Figure 1. Normal endometrium in a 58-year-old woman with vaginal bleeding 6 years after the onset of menopause. Sagittal endovaginal US image shows the uterus (U) with an atrophic, thin endometrium (arrow) measuring 1 mm in thickness. The myometrium (M) has a slightly coarse, speckled echotexture, a common appearance seen in postmenopausal women. Endometrial disease can be excluded with a high degree of certainty; the most likely cause of the bleeding is endometrial atrophy

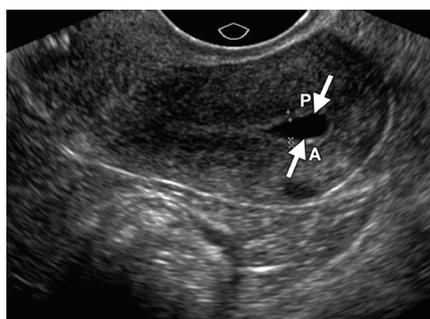


Figure 2. Simple endometrial fluid in a 66-year-old asymptomatic woman with a 3-year history of breast cancer treated with lumpectomy and radiation. Sagittal endovaginal US image shows the uterus with a small amount of simple endometrial fluid (arrows) near the fundus. An endometrial thickness of 1.7 mm was determined by adding 0.7 mm for the anterior (A) layer to 1.0 mm for the posterior (P) layer

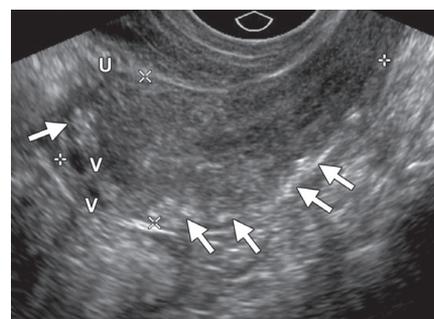


Figure 3. Arcuate vascular calcifications in an 81-year-old woman with postmenopausal bleeding. Sagittal endovaginal US image shows the uterus (U) with extensive arcuate artery calcifications (arrows). The endometrium is was 2 mm thick; this finding was consistent with endometrial atrophy. v = adjacent arcuate veins

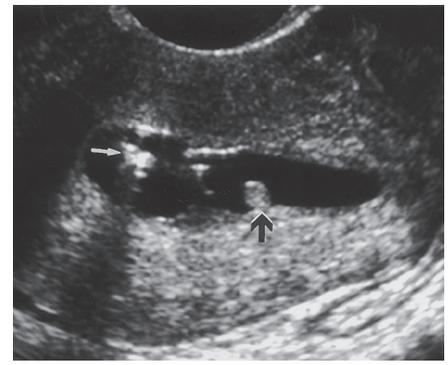
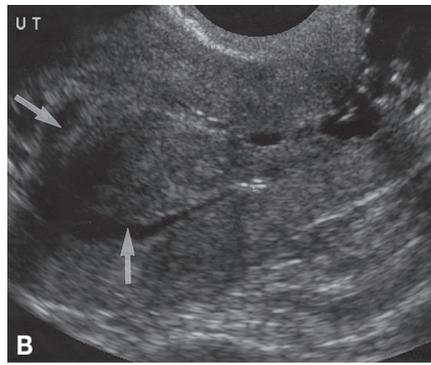
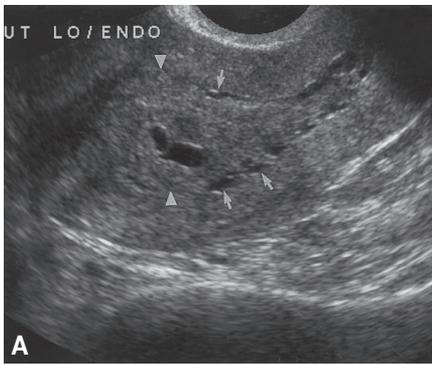


Figure 4. Endometrial thickening associated with tamoxifen therapy. (A) US image reveals marked endometrial thickening (arrowheads) associated with subendometrial cysts (arrows) resulting from tamoxifen therapy. (B) Sonohysterogram demonstrates that the endometrial thickening is secondary to a large polyp (arrows)

Fig 5. Endometrial polyp. Sonohysterogram reveals a small polyp attached by a stalk to the endometrium (black arrow). An echogenic focus in the endometrial cavity (white arrow) represents injected air

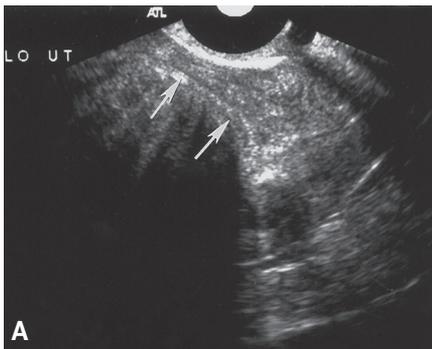


Figure 6. Submucosal fibroid. (A) Endovaginal US image reveals a uterine mass (arrows) with posterior acoustic shadowing. (B) Sonohysterogram reveals that the mass is submucosal in location, a finding that is consistent with an echogenic fibroid

that regardless of symptoms, an endometrial thickness of 5 mm or less is associated with benign histopathologic findings in most cases. This threshold serves as a useful guide for determining which patients should undergo endometrial biopsy. The risk of missing an endometrial abnormality with use of a single measurement of 5 mm or less at endovaginal US is low, with a 99% negative predictive value for endometrial cancer. Therefore, postmenopausal patients who present with vaginal bleeding and have an endometrial thickness of 4–5 mm or greater should be referred for further evaluation to exclude endometrial carcinoma. In postmenopausal patients without abnormal bleeding, most experts advocate tissue sampling only when the endometrial thickness exceeds 8 mm, as the risk of clinically significant endometrial abnormalities in these patients is low. In postmenopausal patients without vaginal bleeding and with an

endometrial thickness from 5 to 8 mm, treatment should be based on individual symptoms and risk factors. Because endovaginal US can be used to accurately assess the endometrium, sequential US examinations can be of value for close monitoring of endometrial thickness.

Hormone replacement therapy affects the thickness of the endometrium. Sequential estrogen and progesterone therapy, often used in perimenopausal patients, induces cyclical endometrial changes and symptoms similar to those occurring in premenopausal patients. In such cases, US scans should be obtained early in the cycle or near the end of withdrawal bleeding, when the endometrium should be at its thinnest. The use of continuous estrogen and progesterone regimens leads to endometrial atrophy; therefore, measurements of endometrial thickness in these patients are usually within the normal range. Unopposed estrogen therapy is associated with

an increased risk of endometrial hyperplasia or carcinoma and is typically prescribed only for women after hysterectomy.

Tamoxifen has been proven effective for the treatment of breast cancer but is associated with increased incidence of endometrial disease among postmenopausal women because of its proestrogenic effect on the uterus. Several studies have shown a direct correlation between the use of tamoxifen and an increase in endometrial thickness, most notable beyond 3 years of therapy. Nearly half of all postmenopausal women undergoing tamoxifen therapy have an endometrial thickness greater than 8 mm, and most are asymptomatic, without abnormal vaginal bleeding. The most common histopathologic findings, including hyperplasia and polyps, are benign, with an approximate 1% risk of endometrial carcinoma. Because endometrial thickening is commonly due to benign causes in patients receiving tamoxifen therapy, there is no clear consensus about a threshold thickness for recommending endometrial sampling in asymptomatic women. The generally accepted rule is that an endometrium <5mm in thickness is normal, 5–10mm borderline and >10mm abnormal, the latter requiring endometrial biopsy even in the absence of vaginal bleeding. However, endometrial biopsy is also performed in those patients on tamoxifen therapy who develop vaginal bleeding and have an endometrial thickness >5mm.

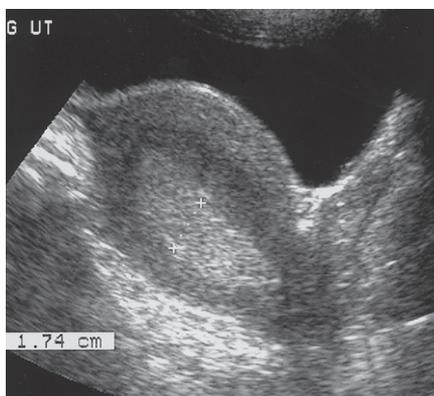


Figure 7. Endometrial hyperplasia. US image shows an endometrium with diffuse thickening (maximum thickness, 1.74 cm) due to hyperplasia (cursors). This finding was confirmed at biopsy.

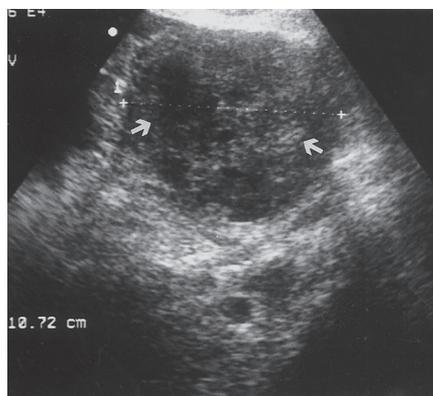


Figure 8. Endometrial adenocarcinoma. US image reveals a heterogeneous endometrial mass (arrows) that is difficult to distinguish from the myometrium. Cursors indicate the entire transverse width of the uterus.

Tamoxifen causes the endometrium to appear thickened, irregular, and cystic at US (Fig 4). The punctate cystic spaces may be secondary to reactivation of adenomyosis within the inner myometrium or to obstructed glands in the endometrium due to the drug's weak estrogenic effects. It has also been reported that the degree of endometrial thickening corresponds to the duration of tamoxifen therapy.

One of the most common reasons to perform pelvic US is postmenopausal bleeding. Causes of postmenopausal bleeding include endometrial atrophy (approximately 75% of cases), endometrial polyps, submucosal fibroids, endometrial hyperplasia, endometrial carcinoma (approximately 10%), and estrogen withdrawal. Imaging should take place immediately after bleeding has stopped, when the endometrium is presumed to be thinnest and any disease entity will be most prominent. Endometrial thickness less than 4–5 mm at endovaginal US generally excludes cancer. Any thickness greater than 5 mm in the setting of postmenopausal bleeding or any endometrial heterogeneity or focal thickening seen at endovaginal US should be investigated further with sonohysterography, biopsy, or hysteroscopy.

Endometrial polyps are a common cause of postmenopausal bleeding and are most frequently seen in patients receiving tamoxifen. Although endometrial polyps may be visualized

at endovaginal US as nonspecific endometrial thickening, they are frequently identified as focal masses within the endometrial canal. Polyps are best seen at sonohysterography and appear as echogenic, smooth, intracavitary masses outlined by fluid (Fig 5).

Uterine fibroids (or leiomyomas) are benign myometrial tumors that occur in patients of all ages. Although their size and frequency increase with age, they may grow until menopause and then involute and are a cause of premenopausal uterine bleeding. They are commonly identified at US as hypoechoic solid masses, but they may be heterogeneous or hyperechoic, depending on the degree of degeneration and calcification. Fibroids may interrupt the endometrium if found in a submucosal location. They are best visualized at sonohysterography (Fig 6) or hysterosalpingography.

Endometrial hyperplasia is an abnormal proliferation of endometrial stroma and glands and represents a spectrum of endometrial changes ranging from glandular atypia to frank neoplasia. A definitive diagnosis can be made only with biopsy, and imaging cannot reliably allow differentiation between hyperplasia and carcinoma. Up to one-third of endometrial carcinoma is believed to be preceded by hyperplasia.

All types of endometrial hyperplasia (cystic, adenomatous, atypical) can cause diffusely smooth or, less commonly, focal hyperechoic

endometrial thickening (Fig 7). The US appearance can simulate that of normal thickening during the secretory phase, sessile polyps, submucosal fibroids, cancer, and adherent blood clots. Endometrial hyperplasia is considered whenever the endometrium appears to exceed 10 mm in thickness, especially in menopausal patients, although it can be reliably excluded in these patients only when the endometrium measures less than 6 mm.

Endometrial hyperplasia may also cause asymmetric thickening with surface irregularity, an appearance that is suspicious for carcinoma. Because endometrial hyperplasia has a nonspecific appearance, any focal abnormality should lead to biopsy if there is clinical suspicion for malignancy.

Endometrial adenocarcinoma is the most common invasive gynaecologic malignancy, but thanks to early detection and treatment, it is not a leading cause of cancer death. US signs of endometrial carcinoma include heterogeneity and irregular endometrial thickening (Fig 8). These signs are nonspecific and can be seen in endometrial hyperplasia as well as polyps, leading to biopsy of almost any irregularity in the setting of postmenopausal bleeding. However, polypoid tumors tend to cause more diffuse and irregular thickening than a polyp and more heterogeneity than endometrial hyperplasia. A more specific US sign is irregularity of the endometrium-myometrium border, a finding that indicates invasive disease. A small amount of fluid in the endometrial canal is likely to be related to benign cervical stenosis and does not require further evaluation. A large intrauterine fluid collection in a postmenopausal patient, although possibly related to cervical stenosis, should raise concern for endometrial (or cervical) carcinoma.

This article outlines the normal findings seen on ultrasound of the endometrium in peri and postmenopausal women and concludes by identifying the most commonly encountered disease entities and their sonographic features. S

# “What’s for dinner tonight?”

This is most probably the most frequently asked question before we leave home to kick out for the day. It is amazing how the human mind gears in anticipation for an event that will take place much later in the day. Whenever I raise this question, although early in the day, I sense that appeal, taste and often the imaginary dish in anticipation of that welcoming evening meal after a day’s work. In today’s day and age however, lack of time is becoming more crucial for the preparation of healthier food for our daily nutrition. We are confronted with numerous instant, off-the-shelf, in-the-pack, from-the-freezer, just-add-water, microwavable ready-made food options that although claim to be with no added sugars, low salt, no MSG, % less fats, no GMOs, organic and whatever can be printed and labelled on the packing, will never come any close to that nutritious meal we are supposed to benefit from.

Here are a few of my smarter tips for easier, tastier, healthier meals every day.

## My 12 mins carrot and pumpkin soup (serves 4)

1. Roast 1 kgs fresh carrots and fresh pumpkin with some onions and garlic
2. Add 1ltr mineral water and grind some salt and pepper
3. Boil for about 5 mins
4. Let set for 3 mins and blend with electric blender
5. Serve immediately with a drizzle of olive oil and some grated orange peel

## My 15 mins grilled salmon, tomatoes, spinach and mushrooms (serves 2)

1. Wash 12 spinach leaves and steam in pot with 2 table spoons water for 5 mins
2. In a grill pan, grill whole cherry tomatoes, and quarter mushrooms until golden.
3. Add 2 fresh salmon steaks and grill for 2 mins on each side with the vegetables
4. Drain the spinach and season with olive oil, salt and pepper
5. Serve the spinach topped with salmon steak surrounded with the vegetables



MASSIMO AZZOPARDI

## My 20 mins oven omelette (serves 2)

1. Boil 2 medium sized potatoes while pre-heating oven to max 300 degrees.
2. Brush a square baking dish with 1 teaspoon oil
3. Beat 3 eggs, add 50ml milk and 1 teaspoon mustard together until well blended.
4. Stir in some chopped onion, grated cheese, salt and paprika and pour in dish.
5. Bake until eggs are set and serve with boiled potatoes sprinkled with fresh chopped parsley

## My 5 mins warm tuna salad (serves 2)

1. Toss some fresh salad leaves in a heated pot with some drops of olive oil
2. Add 2 tins tuna drained from brine
3. Add some green olives, cherry tomatoes and some washed capers
4. Toss well keeping a very low flame for less than 1 minute
5. Serve immediately with quartered boiled egg and some grissini sticks

## My 20 mins bean, tomato and olive tagine (serves 4)

1. Light fry 1 chopped onion, add ½ teaspoon ginger, 1 teaspoon cinnamon
2. Add 500 grms soft cherry tomatoes and cook for 5 mins
3. Add 100 grms un-drained tinned butter beans and about 12 black pitted olives
4. Cook covered for about 15 mins on medium heat and simmer for 2 mins
5. Serve in bowls with some Maltese toasted bread on the side

## My 30 mins beef kofta with egg and tomato (serves 2)

1. Stir fry 500 grms lean beef mince with some onions and garlic in a pan
2. Season with some mixed spice
3. Pour in 300 ml of fresh peeled tomatoes or fresh juiced tomatoes
4. Add 3 fresh eggs each one placed close to the rim of the pan
5. Serve when eggs are cooked. Can be served with boiled rice

## My 15 mins lemon chicken with artichoke hearts (serves 2)

1. Light fry onion and garlic until golden
2. Add 400 gm sliced fresh chicken breast until browned on all sides for 5 minutes.
3. Add 8 (tinned) artichoke hearts and cook for about 3 minutes.
4. Add ½ lemon juice and ½ glass white wine and cook for 2 minutes
5. Remove from heat, stir with some basil and grated lemon rind, and serve

## My 5 mins quick couscous (serves 4/5)

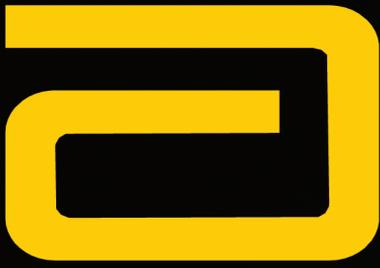
1. Boil 500 ml of water, add a knob of butter and remove from heat
2. Pour in 500 grms of couscous, cover and set aside
3. Chop 2 sun-dried tomatoes, some raisins and some ham
4. Check couscous has absorbed all the hot water and whisk well with a fork
5. Add chopped items, 1 tablespoon tomato paste and stir well to serve hot or cold

We are always encouraged to eat a varied and well balanced diet in moderate portions, drink more water and engage in regular physical activities. 



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145

1 tablet per day. Simplified dosing regimen favours patient compliance

145

At any time of day (irrespective of food)

145

No dose adjustment is required when replacing Fenofibrate 200mg with Lipanthyl 145mg<sup>(1)</sup>

1. SmPC in force

**LIPANTHYL**  
FENOFIBRATE

THERE IS MORE TO IT THAN YOU THINK

**Lipanthyl® 145mg**: white, film-coated tablets. **Indication**: as an adjunct to an appropriate diet and other non-pharmacological treatment, (eg. exercise, weight reduction) for the following: treatment of severe hypertriglyceridaemia with or without low HDL cholesterol levels; mixed hyperlipidaemia when a statin is contraindicated or not tolerated; mixed hyperlipidaemia in patients at high cardiovascular risk in combination with a statin when triglycerides and HDL cholesterol levels are not adequately controlled. **Dosage**: The recommended dose is one 145mg tablet of fenofibrate per day. No dose adjustment is required in elderly; dose must be reduced in patients with renal failure. **Contra-indications**: Liver failure, renal failure, children (under 18yrs), hypersensitivity to fenofibrate or any of the excipients, known photoallergy or phototoxic reaction during treatments with fibrates or ketoprofen, gallbladder disease, chronic or acute pancreatitis, (except acute pancreatitis resulting from hypertriglyceridaemia), patients hypersensitive to sucrose, peanut or arachis oil or soya lecithin or related products. **Special warnings and precautions for use**: Secondary cause of hypercholesterolaemia, such as unregulated Type 2 diabetes, hypothyroidism, nephrotic syndrome, dysproteinemia, hepatic cholestasis, pharmacological treatment or alcoholism, should be appropriately treated; for hyperlipidaemic patients taking estrogens or contraceptives containing oestrogens it is important to verify whether the hyperlipidaemia is of primary or secondary nature. **Liver function**: as with other hypolipidaemic drugs an increase in transaminase was observed in certain, in the majority increases were temporary, minor and asymptomatic; treatment should be stopped if aspartate aminotransferase (AST) levels or serum alanine aminotransferase (ALT) levels show an increase of more than three times the upper limit of normal. If symptoms indicative of hepatitis appear (eg. jaundice or pruritus), lab tests should be done for verification and stopping treatment should be considered. **Pancreatitis**: one case of pancreatitis has been reported in patients taking fenofibrate. **Muscle**: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported during administration of fibrates and other hypolipidaemic drugs. Patients at risk of myopathy or rhabdomyolysis, including patients over 70 years of age or those with a personal or family history of hereditary muscular disease, deterioration in renal function or who suffer from hypothyroidism or consume large amounts of alcohol, run a greater risk of developing rhabdomyolysis. For these patients, the benefit-risk ratio of treatment with fenofibrate should be carefully evaluated. The risk of muscle toxicity may increase if the drug is administered in conjunction with another fibrate or an HMG-CoA reductase inhibitor (statins), especially in cases of pre-existing muscular disease. **Kidney function**: treatment should be interrupted in case if creatinine levels increase to > 50% of the ULN (upper limit of normal). This drug contains lactose. As a result, patients with congenital galactose intolerance, a syndrome classified by the malabsorption of glucose and galactose or a deficiency in lactase, should not take this medicine. Due to the presence of sucrose, this drug should not be taken by patients with fructose intolerance, malabsorption of glucose and galactose or a sucrose-isomaltase deficiency. Lipanthyl 145 mg in coated tablet form should not be prescribed for patients with allergies to peanuts, peanut oil, soya lecithin or any of their derivatives, given the risk of hypersensitivity. **Interactions**: **Oral anticoagulants**: combining fenofibrate and oral anticoagulants is not recommended. Indeed, fenofibrate increases the effect of the oral anticoagulants and can increase the risk of bleeding. However, if this combination is necessary, the anticoagulant dosage should be reduced by one third at the start of treatment and if necessary, readjusted gradually based on the INR. **Cyclosporin**: a few serious, yet reversible cases of renal damage were reported where fenofibrate and cyclosporin were administered together. Renal function in these patients should be carefully monitored and treatment with fenofibrate stopped in the event of significant disturbances to biological parameters. **HMG-CoA reductase inhibitors and other fibrates**: the risk of severe muscular toxicity increases if fenofibrate is administered in conjunction with HMG CoA reductase inhibitors or other fibrates. This combination should be used with the greatest of caution, while keeping a keen eye out for signs of muscular toxicity. **Cytochrome P450 enzymes**: During in vitro studies conducted on the microsomes of human liver, it was shown that fenofibrate and fenofibric acid are not inhibitors of isoforms CYP3A4, CYP2D6, CYP2E1 or CYP1A2 of the cytochrome (CYP) P450. On the other hand, they are slight inhibitors of CYP2C19 and CYP2A6 and slight to moderate inhibitors of CYP2C9. In therapeutic concentrations, Patients receiving a combination of fenofibrate and drugs with a narrow therapeutic margin metabolised by CYP2C19, CYP2A6, and particularly CYP2C9, should be carefully monitored and, if necessary, their dose of these drugs should be adjusted. **Pregnancy and lactation**: no data is available on the use of fenofibrate in pregnant women. Trials conducted in animal did not show evidence of teratogenic effects. However embryotoxic effects were observed at doses corresponding to those of maternal toxicity. The potential risk in humans is thus unknown. Thus, Lipanthyl 145 mg should only be used during pregnancy after a careful evaluation of the benefit-risk ratio has been done. There are no data on the absorption of fenofibrate and/or its metabolites in breast milk. As a result, Lipanthyl 145 mg should not be used while breastfeeding. **Adverse effects**: The adverse effects most frequently reported during treatment with fenofibrate were digestion, gastric and intestinal problems. These included abdominal pain, nausea, vomiting, diarrhoea, and flatulence of moderate intensity. Uncommon symptoms included headaches, thromboembolism (pulmonary embolism, DVT), pancreatitis, gall stones, skin hypersensitivity (rash, itching, hives), muscular disorders (myalgia, myositis, muscle cramps and weakness), sexual dysfunction, increased creatinine levels. Rare adverse effects include: low haemoglobin levels, low leukocyte levels, hypersensitivity, hepatitis, alopecia, photosensitivity reactions and increased urea in the blood. In addition to these events reported during clinical trials, the following adverse effects were spontaneously reported during post-marketing use of Lipanthyl 145 mg. An exact frequency cannot be determined based on the available data and is therefore classified as "unknown": - R respiratory, thoracic and mediastinal disorders: interstitial lung disease. Musculoskeletal, connective tissue and bone disorders: rhabdomyolysis. **Overdose**: Only a few isolated cases of overdose with Fenofibrate were reported. In the majority of cases, no symptoms were reported. No specific antidote is known. If an overdose is suspected, symptoms should be treated and corrective therapeutic measures should be undertaken. Fenofibrate cannot be used in haemodialysis. **Instruction for use/handling**: None. **Licence Holder**: Laboratoires Fournier S.A. **FRANCE AA number**: AA1166/00101