Issue 05/10

Newspaper post

TheSynapse

The Medical Professionals Network

Exclusive

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Editor's word

In this editorial I will focus on one of biggest challenges which scientists are facing … vaccines. Actually vaccines represent one of the most successful cost-effective medical advances of all time.

Nowadays recent advances in biotechnology (as well as the understanding of the inductive and effector components of immune responses) are invigorating the whole field of vaccinology. In fact other illnesses are now slowly but steadily becoming the new targets in this field, with the dual possibility of marketing either therapeutic vaccines (ex. oncology) or prophylactic vaccines (ex. HPV).

These new advances are basically based on either innovative antigens or the introduction of new adjuvants. We are already seeing several new plant-made vaccines being manufactured for veterinary purposes such as the Newcastle disease. However it is in this area that researchers are also eyeing what I call 'virgin platforms' …. the application of plant recombinant technology to the field of human medicine. The former has already brought about major advances in plant biology, allowing production of genetically modified (GM) plants. To be truthful, such progression has also meant headaches for key political champions … just a few weeks ago we have seen uproars surrounding the decision of our European Commissioner for Health and Consumer Policy, John Dalli to lift a 13-year ban on the cultivation of a GM potato, called Amflora, to be used for starch by industry.

Nonetheless, such newer technologies have also enabled the development of noncrop plants (tobacco) to produce pharmaceutical molecules. This approach has major advantages in terms of speed, costs and safety. And this goes beyond the much advertised US creation of the lycopene-rich GM tomatoes which presumably protect against prostatic cancer, way back in 2002 … and six years later, the development by the Brits of the purple tomato, which is also rumoured to reduce cancer risk ….

However, an innovative application of plants as bioreactors is their use to express antigenic molecules to be administered as vaccines. Major potential advantages of producing immunogens in plant systems include the possibility of enabling the participation of less developed countries in pharmaceutical production, with an obvious emphasis on addressing local health issues. Examples of such scientific breakthrough are the recent production in tobacco of a H1N1 2009 vaccine based on the hemagglutinin (HA) protein and the initiation of clinical trials with a recombinant, plant-derived, idiotype vaccine to treat B-cell lymphomas.

In case you are just saying … Well, this is just an editorial for all its worth! … scientists' grapevine has it that the next pandemic may quite likely be the Chikungunya virus. The virus, usually transmitted by Aedes aegypti mosquitoes, has now repeatedly been associated with a new vector, Ae. Albopictus (Asian Tiger Mosquito, seen in Malta during the past few weeks). Analysis of full-length viral sequences reveals an extremely rare phenomenon, known as evolutionary convergence. In virology, convergent mutations have been reported under the extreme selective pressure of antiviral therapy during the treatment of acute (ex. neuraminidase mutations of influenza virus) or chronic (ex. reverse-transcriptase/protease mutations of HIV) viral diseases. Apparently the selective pressure exerted on Mosquito-transmitted Chikungunya virus through the constraint of having to replicate in a new vector, is similar to that cited for antiviral therapy.

And since the dispersal of the Asian Tiger Mosquito from Asia to Europe is largely the result of human activities (such as the commercial transportation of scrap car tyres), the adaptation of Mosquito-transmitted Chikungunya virus to the Asian Tiger Mosquito provides an incredible demonstration of how viruses can readily circumvent the impact of human interference on the ecosystem. Obviously this means that we are far from immune from future emerging arboviruses that infect humans.

Ian C Ellul

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Issue Guide

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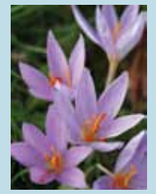
Adonis annua L. (Pheasant's eye, Ghajn is-Serduk)



Adonis annua L. is a scarce, annual, winter and spring flowering herbaceous plant which prefers disturbed ground.

Medicinal uses
It has been used in medicines as a diuretic, as a tonic to improve health, and as a cardiostimulant.

Photography: Guido Bonett ARPS AMPS
Reference: Lanfranco G. Hxejjex medicinali u ohrajn fil-gzejjer Maltin. Media Centre Print; Malta. 1993.

European Society of Cardiology 2010 Clinical Practice Guidelines on Atrial Fibrillation

An Update on Classification and Pharmacotherapy

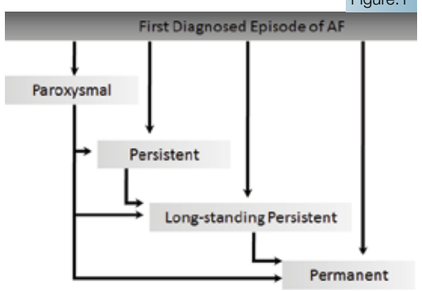
Abstract
The European Society of Cardiology guidelines published in 2010 offer an update on the previously published 2006 atrial fibrillation guidelines. The revisions are intended to optimize the understanding of the mechanisms of atrial fibrillation, and consequently the diagnosis and management of this common sustained cardiac arrhythmia, which afflicts up to 1-2% of the general population.
Ongoing research into the pathophysiology of atrial fibrillation and innovations in pharmacotherapy have forced a revised set of non-mandatory but advisory recommendations to guide clinicians and cardiologists along the challenging labyrinth which is atrial fibrillation management and diagnosis. The purpose of this synopsis is to highlight some of the most relevant changes included in the 2010 guidelines in so far as classification and pharmacotherapy of atrial fibrillation is concerned.

Atrial fibrillation, arrhythmia, heart failure, heart disease

Introduction
The European Society of Cardiology (ESC) guidelines published in 2010 offer an update on the previously published 2006 atrial fibrillation (AF) guidelines. The revisions are intended to optimize the understanding of the mechanisms of AF, and consequently the diagnosis and management of this common sustained cardiac arrhythmia, which afflicts up to 1-2% of the general population.1

Mechanisms of Atrial Fibrillation
The structural remodeling that occurs in the ventricles and atria is the end result of many forms of structural heart disease. Within the atria this translates into proliferation and differentiation of fibroblasts into myofibroblasts and accumulation of surplus connective tissue with eventual fibrosis. These changes produce an electroanatomical substrate which is pervious to multiple small re-entrant circuits and which therefore permits the propagation of AF. Following the onset of AF, the atrial effective refractory period has been shown to shorten within the first days of its onset in addition to a disruption of the normal atrial contractile function.

Figure.1



AF clinical types
The diagram illustrates how a first diagnosed episode of AF may turn out to be any of the 4 clinical sub- types and how the AF categories are not mutually exclusive with patients having paroxysmal AF sometimes moving on to having persistent AF, so on and so forth.
AF=atrial fibrillation. Adapted from Camm AJ et al.1

Clinical Types of AF
The 2010 ESC guidelines offer a modified nomenclature for classification of the AF clinical types (Figure

1). In particular the guidelines distinguish between:

1) Fist diagnosed AF: which represents the first ever episode of AF at the time of initial presentation irrespective of its duration or symptom severity.
2) Paroxysmal AF: representing AF which self-terminates within a maximum of 7 days (although in most cases self-termination occurs within the first 48 hours).
3) Persistent AF: representing non-self-terminating AF which either lasts longer than 7 days, or which requires pharmacological or electrical cardioversion before this time.
4) Long-standing Persistent AF: refers to persistent AF which has been present for ≥1 year before the implementation of a rhythm control strategy is contemplated.
5) Permanent AF: refers to established, accepted AF where both the patient and physician have opted not to pursue any rhythm control strategies.

Type and Severity of Symptoms
The 2010 guidelines place special emphasis on the presence and severity of AF-related symptoms and recommend tailoring the management of AF in such a way as to achieve maximum possible symptom relief. The European Heart Rhythm Association Score of AF-related symptoms2 (Table 1) provides an unambiguous description of AF-related symptom severity.
Antithrombotic Management of AF
The CHADS2 score (cardiac failure, hypertension, age, diabetes, stroke) risk index3 is recommended in these guidelines as a rapid and initial risk assessment tool for cerebrovascular events and transient ischaemic attacks in patients with non-valvular AF. Any patient having a score ≥2 will benefit from the use of chronic oral anticoagulant therapy (OAC) with a vitamin K antagonist (VKA), aiming to maintain a target international normalized ratio (INR) of 2.5, and a range of 2.0-3.0. The greatest limitation of the CHADS2 score lies in its propensity for classifying a disproportionate number of patients within the 'grey-zone' of moderate risk for cerebrovascular events at a score of 1, thereby plunging many a physician into the much dreaded VKA-versus-aspirin conundrum.
The CHA2DS2-VASc score4 (Table 2) employs a more 'risk

Table 1

EHRA Class	Definition
EHRA Class I	No symptoms
EHRA Class II	Mild symptoms; Normal daily activity not affected
EHRA Class III	Severe symptoms; Normal daily activity affected
EHRA Class IV	Disabling symptoms; Normal daily activity discontinued

EHRA score of AF-related symptoms. Adapted from Kirchhof P et al.2

factor-based' approach to the categorization of patients with non-valvular AF and this scheme is the one most prominently campaigned for by the ESC.
In patients with non-valvular AF, a CHA2DS2-VASc score of ≥2 would argue in favour of OAC therapy. One major risk factor would alone confer such a score, as would alternatively two cumulative clinically relevant but non-major risk factors. In either scenario, use of chronic OAC for thrombophylaxis would be justified.
In summary, the guidelines recommend that with a CHADS2 score ≥2, chronic OAC therapy should be initiated, but in patients scoring a CHADS2 of 0-1, a second more comprehensive risk scoring tool should be employed (CHA2DS2-VASc) to determine whether a subject benefits most from OAC as opposed to Aspirin or no antithrombotic therapy (Figure 2).

The HAS-BLED score5 (Table 3) is recommended as a simple bleeding risk score for AF patients, whereby a score ≥3 indicates high risk and calls for caution with the use of oral VKAs.

Long-term Control of Rate and Rhythm in AF
The 2010 guidelines underscore that ventricular rate control in AF is cardinal in all cases unless the heart rate during AF is naturally slow. Additionally rhythm control may be added on to rate control where the patient remains symptomatic despite adequate rate control; alternatively it may be deemed appropriate to choose rhythm control over rate control as the optimal management strategy based on factors such as younger age, symptomatology and higher activity levels. Broadly speaking, those younger patients with symptomatic paroxysmal AF in the absence of significant structural heart disease are usually earmarked for rhythm control. Conversely, patients with accepted permanent AF are usually scheduled to receive rate control with their designation changing to 'long- standing' persistent AF if a later trial of rhythm control is attempted.
A large body of evidence now exists6-12 to dispel the archaic myth which made rhythm control the unchallenged prime end-point in AF management and which relegated rate control strategies to a lackluster division. This newly-found egalitarianism is fuelled by a new appreciation of the importance of patient-tailored therapy taking into consideration factors such as patient preference, level of physical activity and quality of life scores.

Recommended Drugs for Long-term Rate Control

• Bvetablockers
Particularly in patients with high adrenergic tone or angina in association with AF.
Recommended agents include: Metoprolol, Bisoprolol, Atenolol, Propanolol and Carvedilol.

• Non-dihydropyridine calcium channel blockers
Effective for acute and chronic rate control of AF. These drugs are to be avoided in patients with systolic heart failure in view of their negatively inotropic effect.
Recommended agents include: Verapamil and Diltiazem.
•Digoxin
Effective for heart rate control at rest but not during exercise. The potentially life-threatening adverse effects and propensity for drug interactions ascribed to digoxin dictates a cautious introduction in properly selected patient groups.

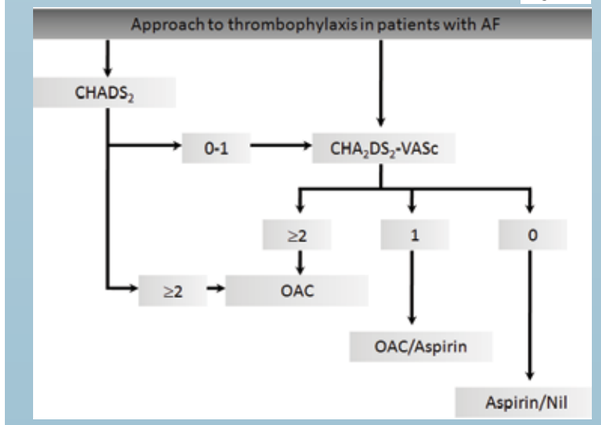
•Dronaderone
Perhaps one of the most noteworthy advances of the 2010 ESC guidelines is the inclusion of the recently approved dronaderone as an alternative rate controlling drug for

Table 2

Risk Factor	Attributable Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes Mellitus	1
Stroke/TIA/systemic thrombo-embolism	2
Vascular disease	1
Age 65-74	1
Sex **C**ategory (female sex)	1
Maximum score	**9**

CHA2DS2-VASc Scoring System.
Maximum possible score using the CHA2DS2-VASc Scoring System is 9.
Major risk factors are displayed inside dark grey cells.
Clinically relevant non-major risk factors are displayed inside light grey cells.
Congestive heart failure is arbitrarily defined as left ventricular (LV) ejection fraction (EF) ≤40%.
Vascular disease encompasses any of: myocardial infarction, complex aortic plaque and peripheral artery disease.
LV=left ventricular; TIA=transient ischaemic attack.

Fig. 2



With a CHA2DS2-VASc score of 1, the recommendations are in favour of either OAC or aspirin 75-325mg daily. With a CHA2DS2-VASc score of 0, the recommendations are in favour of either aspirin 75-325mg daily or no antithrombotic therapy. Adapted from Camm AJ et al.1
AF=atrial fibrillation; OAC=oral anticoagulation;

Table 3

Letter	Clinical Characteristic	Points Attributed
H	Hypertension	1
A	Abnormal Renal Function and/or Abnormal Liver Function	1 1
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65 years)	1
D	Drugs and/or Alcohol	1 1
	Maximum score	**9**

HAS-BLED score adapted from Pisters et al.5

chronic management of AF. It effectively controls ventricular rate both at rest and during exercise with these effects being additive to those of other rate controlling drugs (Dronaderone is not currently approved for rate control in permanent AF.)
Dronaderone is a multichannel blocker active at the sodium, potassium and calcium channels which is also endowed with non-competitive antiadrenergic activity.

•Amiodarone
Effective as a rate controlling agent being particularly suited for intravenous administration in the haemodynamically-ill AF sufferer. It should be considered for long term ventricular rate control only if all other measures have failed and in this context the burden of its innumerable extracardiac adverse events must be borne in mind.

Recommended Drugs for Long-term Rhythm Control
The new 2010 guidelines essentially eliminate quinidine from the rhythm controlling armamentarium of drugs and instead propose dronaderone as one of the emerging therapeutic options for achieving and maintaining sinus rhythm.

•Beta-blockers other than Sotalol
Only modestly effective in preventing recurrent AF except in the setting of thyrotoxicosis and exercise- induced, adrenergic, lone AF where they have a specific and valid role. Their use is limited by contraindications in the presence of significant left ventricular hypertrophy, systolic heart failure and pre-existing QT prolongation.

•Flecainide
Safe in the absence of structural heart disease and contraindicated for use in hearts with impaired systolic function and coronary artery disease.

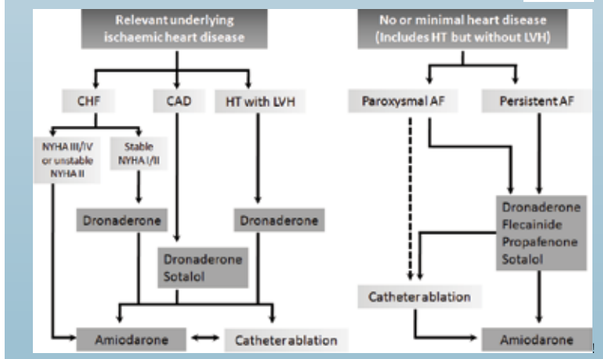
•Propafenone
As for flecainide, propafenone is considered safe in the absence of structural heart disease and contraindicated for use in hearts with impaired systolic function and coronary artery disease.

•Amiodarone
Amiodarone is superior to propafenone and sotalol at preventing recurrent AF and is particularly indicated in symptomatic sufferers where other antiarrhythmic agents have failed to maintain sinus rhythm. It is one of only a few antiarrhythmics which is not contraindicated in the presence of structural heart disease and heart failure. The attendant adverse drug reactions of amiodarone therapy together with its potential interactions with oral VKAs and digoxin beckon watchful vigilance of all patients and their doctors.

•Sotalol
Sotalol has a role in preventing recurrent AF but it's proarrhythmic adverse effects become especially taxing in patients with electrolyte abnormalities, particularly hypokalaemia and hypomagnesaemia. Unlike amiodarone it's use is considered imprudent in patients with structural heart disease and systolic heart failure.

•Dronaderone
Admittedly less effective at maintaining sinus rhythm than amiodarone13,14 but far less toxic to the thyroid gland, central nervous system, skin and eyes, which equates to better tolerability and a smaller incidence of premature drug discontinuation. It is contraindicated in patients with New York Heart Association (NYHA) class III15 or more and in unstable heart failure patients but is considered safe in patients with acute coronary syndromes, chronic stable angina, hypertensive heart disease and stable NYHA class I-II heart failure (Figure 3).

Fig. 3



Summary of recommendation for choice of antiarrhythmic drug therapy in AF patients with and without structural heart disease. Adapted from Camm AJ et al.1
HT=hypertension; AF=atrial fibrillation; CHF=congestive heart failure; CAD=coronary artery disease; LVH=left ventricular hypertrophy; NYHA=New York Heart Association.

Conclusion
Ongoing research into the pathophysiology of AF and innovations in pharmacotherapy have forced a revised set of non-mandatory but advisory recommendations to guide clinicians and cardiologists along the complex labyrinth which is AF management and diagnosis. The purpose of this synopsis was to highlight some of the most relevant changes included in the ESC 2010 guidelines in so far as classification and pharmacotherapy of AF is concerned, while encouraging a more insightful review of the full-text guidance offered by the ESC Committee for Practice Guidelines. For the complete guidelines visit www.escardio.org.

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Focus on

Pediatric Gastroesophageal Reflux Disease

One of the most common complaints referred to primary caregivers in infancy is reflux type emesis in the infant, less frequently and sometimes posing as chest pain and discomfort upon swallowing, reflux can also present in the older child and adolescent. Gastroesophageal reflux disease (GERD) can complicate the management of the child with neurodevelopmental disability wherein a more severe pattern of disease is exacerbated by delayed, sometimes atypical presentation. Moreover, even in otherwise healthy children, there is increasing recognition of non-gastrointestinal presentations of gastroesophageal reflux disease (GERD) that span the gamut from failure to thrive, dental erosion and complicated asthma.

It is important, from the outset, to distinguish physiologic reflux (GER); the passage of gastric contents into the esophagus with or without regurgitation into the mouth, which is a normal process occurring several times a day in, amongst others, healthy infants from Gastroesophageal Reflux Disease (GER); wherein refluxate causes troublesome symptoms (Table 1).

Infancy	Older Child and Adolescent
Recurrent regurgitation with/without vomiting Weight loss or poor weight gain Irritability Ruminative behavior Stridor Cough Hoarseness Apparent life-threatening events & Apnea spells Dystonic neck posturing (Sandifer syndrome) Feeding refusal Recurrent pneumonia	Bitter regurgitation Vomiting Heartburn or chest pain Hematemesis Dysphagia, odynophagia Wheezing Stridor Cough Hoarseness Recurrent pneumonia Anemia Dental erosion

Table 1. Symptoms and signs that may be associated with gastroesophageal reflux disease

GERD is a clinical diagnosis; there is no gold standard investigation, indeed in most uncomplicated cases clinical interview and examination are sufficient. This can be supplemented with an empiric therapeutic trial obviating the need for any further investigations.

There is mounting evidence to support a role of GERD in diverse disease processes including respiratory disease including recurrent pneumonia and atypical asthma, dental erosion and, with less robust evidence; upper airway complaints such as hoarseness, chronic cough, recurrent sinusitis, otitis and the sensation of a lump in the throat (globus). It is also important to bear in mind that GERD is more prevalent in obese children and is associated with greater severity of disease including the development of Barrett's Esophagus and adenocarcinoma in adults.

In cases where a diagnostic workup is needed, for example in children with atypical presentations or who are refractory to standard, or first line management, the choice for investigation falls between upper endoscopy with biopsy – which serves to rule out a gamut of alternative diagnoses based on gastrointestinal pathology (Table 2), and pH or impedance probe. Radiologic modalities such as upper gastrointestinal contrast study (barium meal) and nuclear scintigrapy scan (milk scan) are limited in scope but useful in select clinical scenarios including the need to rule out malrotation and duodenal stenosis (Barium meal – Fig 1) , or reflux and aspiration or delayed gastric emptying (Milk scan).

Gastrointestinal obstruction	Infectious
Malrotation with intermittent volvulus	Otitis media
Pyloric stenosis	
Intestinal duplication	Metabolic/endocrine
Hirschsprung disease	Galactosemia
Antral/duodenal web	Congenital adrenal hyperplasia
Foreign body	
Incarcerated hernia	Renal
	Obstructive uropathy
Other gastrointestinal disorders	
Gastroenteritis	Cardiac
Peptic ulcer	Congestive heart failure
Eosinophilic esophagitis/gastroenteritis	
Food allergy	Toxic / Medications
Inflammatory bowel disease	Iron hypervitaminosis A and D
Neurologic	Munchausen syndrome by proxy
Hydrocephalus	
Migraine	Cyclic vomiting syndrome
Intracranial mass	
Chiari malformation	Autonomic dysfunction

Table 2. Differential diagnosis of vomiting in infants and Children

Continues on page 12

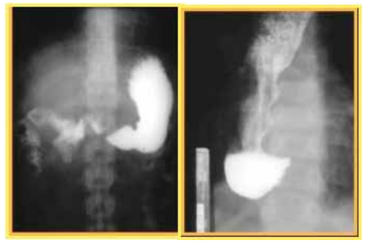

Figure 1. (A) Intestinal malrotation in an 8 year-old with chronic vomiting and heartburn. (B) Achalasia in a 14 year-old girl with chronic vomiting. Previous diagnosis 'psychogenic vomiting'

FOR INFANTS	FOR OLDER CHILDREN
Normalize feeding volume and frequency	Avoid large meals
Consider thickened formula	Do not lie down immediately after eating
Positioning	Lose weight, if obese
Consider trial of hypoallergenic formula	Avoid caffeine, chocolate, and spicy foods that provoke symptoms
	Eliminate exposure to cigarette smoke

Table 3. Lifestyle changes for GERD

The management of GERD depends on the consequences of the disease and associated conditions. Longstanding severe GER can lead to scarring and difficulty swallowing as well as transformation of the lower esophageal mucosa into premalignant, intestinal mucosa (Barrett's Esophagus). This latter is rare in children, although the presence of neurodisability and hiatus hernia may be possible risk factors.
Reassurance, education and conservative measures are all that is needed in most cases of infant GERD; lifestyle changes (Table 3) may include a switch to an antireflux formula (AR) although the presence of physiologic GER should not be construed as a justification to stop breastfeeding. First line pharmacologic therapy include the use of ranitidine 2mg/kg/dose three times daily, although locally the liquid formulation (15mg/ml) is only available though the government pharmacy. Although well established for use in infants and children, the emergence of tachyphylaxis as well as the limited acid suppression achievable with Histamine-2 Receptor Antagonists (H2RA) including ranitidine, resulted in now fairly routine use of proton-pump inhibitor agents (PPI) in this age group. Several are licensed for use in children, the usual dose is 1mg/kg / day and the most frequent, usually dose-dependent side effects are headache, diarrhea, constipation and nausea. Although unlicensed for use in infants, PPI agents are increasingly used and are generally thought to be safe although, for obvious reasons, the choice is limited to soluble formulations. The routine use of prokinetics in the long term management of GERD in children is not recommended based on the unfavourable risk-benefit relationship.

Surgical options in the management of GERD are, in most clinical scenarios, limited to the last resort. A variety of different techniques for fundoplication purport to recreate or strengthen the physiologic lower esophageal sphincter. Decreased reflux is often achievable but at the risk of several potential long term complications that tend to be more common in younger age at the time of operation and concomitant neurodisability. An alternative surgical option, especially in the latter subgroup of patients includes gastrostomy placement, which facilitates continuous (therefore low volume) feeds, and in rare cases jejunostomy feeds. Endoscopic fundoplication, which is established in adult medicine, is as yet unavailable in children.

Gastroesophageal reflux therefore emerges as a relatively common complaint in the peadeiatric population. In select scenarios the index of suspicion needs to be heightened and despite tremendous progress in the diagnostic modalities, investigation and treatment needs to be individualized and preferably center around conservative and safe measures.

Soy Proteins:

metabolic effects and role in the cardiovascular prevention

Several epidemiological studies have proved that elevated plasma levels of total and, in particular, low-density lipoprotein (LDL) cholesterol are associated with an increased risk of coronary and, in general, cardiovascular events. More recently, many controlled studies undertaken with dietary or pharmacological interventions have demonstrated that reduced plasma levels of total and LDL cholesterol (LDL-C) result in a decreased incidence of such events.
The risk reduction is strongly related to the magnitude of the decline in LDL-C.
An 1% decrease in plasma levels of total or LDL-C is followed, on average, by a 1% risk-reduction. Moreover, the effect on cardiovascular risk appears to be independent of the methods used to achieve a lower plasma cholesterol level.

Soy-derived protein displayed significant cholesterol-lowering activity in clinical studies that involved patients with different forms of hypercholesterolemia. Some studies reported that soy protein, when partially or fully substituted for dietary animal protein, induced a mean decrease of 22 mg/dl in LDL-C concentrations with a dosage of 20-30 g/day and a decrease of 90 mg/dl with a dosage of 30-50 g/day. The observed reduction was related to the initial plasma cholesterol concentrations, that is it was greater in subjects with established hypercholesterolemia and minor or negligible in those with baseline cholesterolemia below 230 mg/dl.

The most effective cholesterol-lowering soy component is almost certainly protein, whereas isoflavones do not appear to contribute significantly to the effects on lipid metabolism. The cholesterol-lowering effect may be attributable to the ability of soy protein to upregulate the expression of apo-B receptors.
Based on the available scientific evidence, in 1999 the US FDA released a claim that a daily dietary supplementation with four soy-protein servings (6.25 g each) may significantly reduce the risk of cardiovascular disease.

Appropriate assessment of the dietary lipid intake is also important to meet an adequate daily calcium requirement. Milk and dairy products (yogurt, cheese, and ice cream) represent the major source of calcium. This issue is crucial, in particular for women who need to prevent osteoporosis and its complications as well as to prevent coronary heart disease through the control of plasma cholesterol levels. Is therefore advisable to adopt a diet with adequate calcium content while at the same time limiting the total lipid intake. A soy based diet could be recommended.

The use of soy can also positively influence health-related parameters other than the lipid profile, such as diabetes and insulin sensitivity because the shift of calories from carbohydrates to calories from soy is currently adopted as dietary therapy for the metabolic syndrome and type II diabetes, as it reduces plasma triglyceride levels without influencing negatively plasma HDL cholesterol levels.

In overweight and obesity area the consumption of soy proteins could generate effect of satiety and in hypertensive patients the daily intake of 25 g/day could generate a 2-5 mmHg blood pressure lowering.

In conclusion the use of soy can represent an appropriate base for a nutritional strategy aimed to prevent cardiovascular diseases. The effect of such a dietary model on cholesterol levels can be enhanced, whenever necessary, by soy protein full substitution for dietary animal protein.

Focus on

Mosquito transmitted viral diseases

An update on Europe and the Mediterranean Basin

By Tanya Melillo

Mosquitoes are insects that have a particular importance in public health as they are vectors of major viral diseases like Dengue, Chikungunya and West Nile fever and can constitute a nuisance to the population.

Dengue and Chikungunya viruses are endemic in tropical countries and are
transmitted by infected Aedes mosquitoes. During recent years, the incidence of both Dengue and Chikungunya fever has risen worldwide. There is no vaccine available for either of them and prevention relies entirely on mosquito control and personal protection. Besides the international concern over the rising worldwide incidence, there is a specific concern regarding the spread of both diseases within the European Union due to the presence in some of the Member States of the competent vector, Aedes albopictus.

Any cases reported from the EU up till the end of September 2010 were related to imported cases from infected travellers returning from endemic countries outside Europe such as

- All South East Asia, except Korea;
- Western Pacific Region and Pacific islands (like Philippines, Malaysia, Vietnam, Cambodia);
- South America and the Caribbean;
- Sub-Saharan Africa.

The Aedes albopictus (Asian Tiger) mosquito has already been introduced into several European countries, including Belgium, Bosnia and Herzegovina, Croatia, France, Greece, the Netherlands, Serbia and Montenegro, Slovenia, Spain, Italy and Switzerland. It is thought to have occurred through the trade of used tyres (the mosquito lays eggs in pools of water in the tyres) and ornamental plants which are transported in water, such as the 'Lucky bamboo'.

The southern part of Europe is most favourable to climate and ecological conditions for the local establishment of Aedes Aldopcitus and that is why since its first sighting on our islands in September 2009, over the past summer months we have seen its presence in a number of towns. The mosquito normally emerges between May and October and it is during this time that mating and proliferation occurs. Mapping of its distribution is being monitored in Malta and Gozo. The general public is also helping the IDCU by providing IDCU with mosquito samples which are being verified by an entomologist. So far the mosquito has been found in Mellieha, Bugibba, Qawra, St.Paul's Bay, Bahar ic-caghaq, Pembrole, Swieqi, Sliema,Mosta, Bumarrad, Attard, Balzan, San Gwann, Kappara, Floriana, Valletta, St, venera, M'scala and Kalkara.

Outbreaks of Chikungunya have occurred in Europe in the island of La Reunion (South East region of France) in 2006 which resulted in 255,000 cases and 213 deaths over a 10-month period, and in Italy in 2007 which caused 300 cases and 2 deaths over 3 months.
Till the end of September 2010, the Institut de Veille Sanitaire in France reported the first two confirmed cases of locally acquired Chikungunya on the French mainland in two 12 year old girls. This is the first time that a case has been discovered that was not imported.
Since 2005 there have also been reported imported cases of Chikungunya in Germany, UK, Belgium, Czech Republic and Norway.
No Dengue outbreaks have been reported in Europe so far but imported cases have been reported by France, UK, Italy, Spain, Greece and Slovenia. Dengue is being considered as one of the world's major emerging infectious diseases since it has become the most rapid spreading mosquito-borne viral disease in the world with a 30 fold increase in cases over the last 50 years.
In mid-September of this year, the Ministry for Health of France reported a locally acquired case of Dengue fever in Nice.This is the first locally-acquired case of Dengue fever to be reported in mainland Europe since 1928 when outbreaks were reported in Greece.

Another disease, the West Nile fever is transmitted by another mosquito vector, the Culex pipiens which is abundant on our island. The primary hosts are bird and horses. Outbreaks of West Nile fever has been recorded in Italy (1998, 2008, 2009) and this year in Hungary, Romania and Greece. Cases have also been reported in Portugal, France, Spain, Austria, Croatia, Czech Republic, Poland, Russia, Morocco, Tunisia and Israel.

West Nile fever is an emerging disease in southern Europe and is endemic in other parts of Europe and the Mediterranean region. The majority of West Nile fever infections (around 80%) are asymptomatic and only 20% of infected persons will develop mild symptoms with less than 1 % developing a severe neurological syndrome of meningitis and /or encephalitis.

Broad protection against rotavirus gastroenteritis (RGE) caused by the 5 most common circulating rotavirus types[1,2]

RotaTeq™

(Rotavirus Vaccine, Live, Oral, Pentavalent)

RotaTeq is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infection.

In clinical trials, efficacy was demonstrated against gastroenteritis due to rotavirus of serotypes G1P1[8], G2P[4], G3P1[8], G4P1[8], and G9P1[8]

Vaccination with RotaTeq may not result in complete protection in all recipients.

The most commonly reported adverse experiences with RotaTeq (frequency >1/10) include pyrexia, diarrhoea and vomiting.

RotaTeq should not be administered to individuals with hypersensitivity to any component of the vaccine.

No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to immunocompromised patients, those receiving immunosuppressive therapy, individuals infected with HIV, or individuals who have received a blood transfusion or blood products within 42 days of vaccination. Cases of gastroenteritis associated with vaccine virus have been reported post marketing in infants with severe combined immunodeficiency (SCID).

Before administering RotaTeq, please read the full Prescribing Information.

References: 1. Data on file, MSD, Middle East offices. **2.** Centers for Disease Control and Prevention (CDC). Rotavirus Surveillance — Worldwide, 2001–2008. *MMWR Morb Mortal Wkly Rep.* 2008;57(46):1255–1257.

Consider the results. Choose RotaTeq.

MSD

9-11 RTV-2009-MVD-1310402-J

09-2011-RTV-2009-ME-[CY-MA]-1697-J

ROTATEQ ® Rotavirus vaccine (live, oral)
ABRIDGED PRODUCT INFORMATION
Please refer to Summary of Product Characteristics (SPC) before prescribing

PRESENTATION
Oral Solution
2 ml solution in a pre-filled squeezable tube (LDPE), with a twist-off cap (HDPE) in a protective bag, pack size of 1
One 2-ml dose contains:
rotavirus serotype* G1 not less than 2.2 x 106 IU1, 2
rotavirus serotype* G2 not less than 2.8 x 106 IU1, 2
rotavirus serotype* G3 not less than 2.2 x 106 IU1, 2
rotavirus serotype* G4 not less than 2.0 x 106 IU1, 2
rotavirus serotype* P1[8] not less than 2.3 x 106 IU1, 2
* human-bovine rotavirus reassortants (live), produced in Vero cells.
[1] Infectious Units
[2] As lower confidence limit (p = 0.95)
Excipient:
This product contains sucrose 1080 mg

USES: RotaTeq is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infection. In clinical trials, efficacy was demonstrated against gastroenteritis due to rotavirus of serotypes G1P1[8], G2P[4], G3P1[8], G4P1[8], and G9P1[8].The use of RotaTeq should be in accordance with official recommendations.

DOSAGE AND ADMINISTRATION. Posology:
Three doses of RotaTeq should be administered. The first dose may be administered from the age of six weeks and no later than the age of 12 weeks. RotaTeq may be given to infants who were born prematurely provided that the period of gestation was at least 25 weeks. These infants should receive the first dose of RotaTeq at least six weeks after birth. There should be intervals of at least 4 weeks between doses. It is preferable that all three doses should be administered before the age of 20-22 weeks. All three doses should be given by the age of 26 weeks.As no data exist regarding the interchangeability of RotaTeq with another rotavirus vaccine, it is recommended that infants who receive RotaTeq for the first immunisation against rotavirus should receive this same vaccine for the subsequent doses.If it is observed or strongly suspected that an incomplete dose has been swallowed (e.g., infant spits or regurgitates the vaccine), a single replacement dose may be given at the same vaccination visit, however, this has not been studied in clinical trials. If the problem recurs, additional replacement doses should not be given.
No further doses are recommended after completion of the 3-dose series.Method of administration: For oral administration only.RotaTeq SHOULD UNDER NO CIRCUMSTANCES BE INJECTED. RotaTeq may be given without regard to food, liquid, or breast milk.

CONTRA-INDICATIONS:
-Hypersensitivity to the active substance or to any of the excipients.
-Hypersensitivity after previous administration of rotavirus vaccines.
-Previous history of intussusception.
-Subjects with congenital malformation of the gastrointestinal tract that could predispose to intussusception.
-Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of RotaTeq. However, in the absence of sufficient data, administration of RotaTeq to asymptomatic HIV subjects is not recommended.
-Administration of RotaTeq should be postponed in infants suffering from acute severe febrile illness. -The presence of a minor infection is not a contraindication for immunisation. The administration of RotaTeq should be postponed in subjects suffering from acute diarrhoea or vomiting.

PRECAUTIONS
No safety or efficacy data are available regarding administration of RotaTeq to immunocompromised infants, infants infected with HIV or infants who have received a blood transfusion or immunoglobulins within 42 days of dosing.
In trials, RotaTeq was shed in the stools of 8.9 % of vaccine recipients almost exclusively in the week after dose 1 and in only one vaccine recipient (0.3 %) after dose 3. Peak excretion occured within 7 days of dosing. It is theoretically possible that transmission of vaccine virus may occur to seronegative contacts. RotaTeq should be administered with caution to individuals with close contacts who are immunodeficient (e.g., individuals with malignancies or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy). Also, those caring for recent vaccinees should observe careful hygiene especially when handling excreta.In a clinical study, RotaTeq was administered to approximately 1,000 infants who were born at a gestational age of 25 to 36 weeks. The first dose was administered from 6 weeks after birth. The safety and efficacy of RotaTeq were comparable between this subset of infants and infants born at term. Safety or efficacy data are not available for infants with active gastrointestinal illnesses (including chronic diarrhoea) or growth retardation. Administration of RotaTeq may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk. The level of protection provided by RotaTeq is based on the completion of all 3 doses. As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients. RotaTeq does not protect against gastroenteritis due to other pathogens than rotavirus. No clinical data are available on the use of RotaTeq for post-exposure prophylaxis.RotaTeq contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine.
The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.Co-administration of RotaTeq with vaccines containing one or more of the following antigens at approximately 2, 4 and 6 months of age demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected: Diphtheria-tetanus-acellular pertussis vaccine (DTaP), Haemophilus influenzae type b vaccine (Hib), Inactivated poliomyelitis vaccine (IPV), Hepatitis B vaccine (HBV) and Pneumococcal conjugate vaccine (PCV).Co administration of RotaTeq with DTaP-IPV-HBV-Hib vaccine (Infanrix hexa) at approximately 2, 3, and 4 months of age demonstrated that the immune responses and the safety profiles of the co administered vaccines were unaffected compared to separate administrations.
Co administration of RotaTeq with a group C meningococcal conjugate vaccine (MenCC, the vaccine studied was a tetanus toxoid conjugate) at 3 and 5 months of age (and mostly at the same time as DTaP-IPV-Hib vaccine), followed by a third dose of RotaTeq at approximately 6 months of age, demonstrated that the immune responses to RotaTeq and MenCC were unaffected. Co administration resulted in an acceptable safety profile.Concomitant administration of RotaTeq and oral poliomyelitis vaccine (OPV) did not affect the immune response to the poliovirus antigens. Although concomitant administration of OPV slightly reduced the immune response to rotavirus vaccine, there is currently no evidence that clinical protection against severe rotavirus gastroenteritis would be affected. The immune response to RotaTeq was unaffected when OPV was administered two weeks after RotaTeq. Therefore, RotaTeq can be given concomitantly with monovalent or combination infant vaccines containing one or more of the following antigens: DTaP, Hib, IPV or OPV, HBV, PCV and MenCC.

Pregnancy and lactation: RotaTeq is intended for use in infants only. Thus human data on use during pregnancy or lactation are not available and animal reproduction studies have not been performed.SIDE

EFFECTS.Refer to SPC for complete information on side effects
In a subset of infants from 3 placebo-controlled clinical trials (n=6,130 recipients of RotaTeq and 5,560 placebo recipients), RotaTeq was evaluated for all adverse events within 42 days of vaccination with or without concomitant use of other paediatric vaccines. Overall, 47 % of infants given RotaTeq experienced an adverse reaction compared with 45.8 % of infants given placebo. The most commonly reported adverse reactions that occurred more frequently with vaccine than with placebo were pyrexia (20.9 %), diarrhoea (17.6 %) and vomiting (10.1 %).Adverse reactions more common in the vaccine group are listed below per system organ class and frequency. Based on pooled data from 3 clinical trials in which 6,130 infants received RotaTeq and 5,560 received placebo, the adverse reactions listed occurred with excess incidences in RotaTeq recipients compared to placebo recipients of between 0.2 % and 2.5 %.
Infections and infestations
Common: Upper respiratory tract infection
Uncommon: Nasopharyngitis
Gastrointestinal disorders
Very common: Diarrhoea, Vomiting
Uncommon: Abdominal pain upper
Skin and subcutaneous tissue disorders
Uncommon: Rash
General disorders and administration site conditions
Very common: Pyrexia

Intussusception
The risk of intussusception has been evaluated in a placebo-controlled study in infants. During the combined 42-day periods following each dose, there were 6 cases of intussusception in 34,837 recipients of RotaTeq compared with 5 cases in 34,788 placebo recipients.
Post-marketing reports
The following adverse experiences have been spontaneously reported with RotaTeq: haematochezia, urticaria amd apnoea in very premature infants (≤ 28 weeks of gestation).

Marketing Authorisation Number:
EU/1/06/348/001

Marketing Authorisation Holder: Sanofi Pasteur MSD, SNC 8, rue Jonas Salk. F-69007 LYON , France

Rotateq is a registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA

POM
Date of review of prescribing information: June 2009

There is more to *TheSynapse* than just

MedClub Card news

Over the past weeks, many Synapse members have been receiving their MedClub membership card. Please call us on 21453973 if you have applied to become a Medclub member but did not receive your membership card yet.

We are delighted to inform the MedClub members that we have secured further offers exclusive for them.

• **Air Malta** is offering MedClub Members 10% discount when using Air Malta scheduled Services (excluding promotional offers). More details will be announced on TheSynapse Portal in the coming weeks.

• **Corinthia Hotels** are offering 20% discount off Corinthia™ Hotels Best Availability Rate on bookings made directly through www.corinthia.com. To benefit from the discount, MedClub Members must simply present their MedClub card on check-in at any Corinthia Hotel and the discount will be immediately applied to their hotel bill.

• **Tuaco Opticians** are offering 10% discount on Optical Frames, lenses, sunglasses as well as sighted sunglasses, and a 5% discount on contact lenses and contact lens solutions. They are also offering an exclusive 15% discount on high quality designer frames including the brands Prada, Dolce & Gabbana, Salvatore Ferragamo as well as Versace.

• **Bridgestone Tyre Center** in Marsa is offering 10% discount.

These add to the offers that The Synapse has already secured from:
• **Vodafone** - unbeatable packages being offered exclusively to MedClub members;
• **The Athenaeum Spa** - 20% when purchasing a 6 month or annual membership;
• **BDL Bookshop** - 15% off online orders with free delivery;

More information on these offers will be announced on The Synapse Portal in the coming weeks.
The list of MedClub Benefits is always growing so join as a MedClub member and enjoy these discounts too.

Please visit www.thesynapse.net/medclub to apply for your free membership

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COMPETITION CORNER – ISSUE 4/10

This month's Challenge answers

1. What was the biblical name which featured in the Wine Expectations article's quote?
2. The prize given to the first drawn name of the Update and Win quizz was 2 tickets to the Elton John concert?

The winners are: TO BE changed
1st prize - **Ms. Graziella Gravino** (2 tickets to the Wintermoods concert)
2nd prize - **Dr. Michael Refalo** (1 day membership to the Corinthia Athenaeum Spa, Attard)
3rd prize - **Dr. David Muscat** (1 day membership to the Corinthia Athenaeum Spa, Attard)

TheSynapse team would like to congratulate the winners and thank the sponsors of these competitions.

THIS MONTH'S CHALLENGE

The answers to all questions can be found in issue 3/10.Those who get a correct answer will participate in a draw where the first two drawn names will each win a 1 day membership to the Corinthia Athenaeum Spa, Attard.

1. What was the name of the nurse who came up with the idea of the contraceptive pill?

_____

2. Name one disease transmitted by the Asian Tiger Mosquito Yes / No

_____

Fill in your details

Name

Address

Email

Mobile

Kindly submit the answers by mail by filling the form on this page addressed to The Professional Services Centre, 3 Guzi Cutajar Street, Dingli, DGL 1201 or submit your answers on- line on www.thesynapse.net/quizz. All submissions will participate in a draw.
You have up to the 7th November 2010 to submit your answers.

Opportunites

Managing pharmacist Vacancy

Mondays to Thursdays mornings And Friday and Saturday mornings and evenings

Clinic Space available in the morning, Safi Pharmacy

New clinic with all amenities is available in the mornings. Please phone 79060903

Locum Pharmacist Required

Locum Pharmacist required to work two afternoons on a regular basis for St Joseph Pharmacy in Mosta. Any enquiries can be made by phoning 79417593.

Attention Doctors, Consultants and other Medical Specialists

Medical Plaza San Gwann requires the services of locum pharmacists evenings weekdays immediately and Saturdays between 1 and 4 pm as from end December. Kindlly contact Ingrid Fenech on 21372195, 21377157 or 99371724.

Attention Doctors, Consultants and other Medical Specialists

Clinic space available in a central locality, adjacent to a Busy Pharmacy in the village core. No rental fee.
For more information please call 79861544 or 21820795

Locum Pharmacist Required

Opportunity has arisen for a third general practitioner to work out of an established and busy clinic in the north harbour region. Attending also are a number of specialists and therapists, offering a wide spectrum of services to our clients and enabling an efficient and multidisciplinary approach. Kindly contact me on dwardu@yahoo.com

Current / Upcoming Events

Influenza Vaccine Campaign – log on http://www.thesynapse.net/articles/viewarticle.asp?artid=12529

Looking for Melanoma Campaign – log on http://www.thesynapse.net/articles/viewarticle.asp?artid=12397 or contact Dr Joseph Pace for a free referral on guzeppip@gmail.com OR josephlpace@onvol.net. Terms & conditions apply.

Breast Cancer Awareness Campaign – log on http://www.sahha.gov.mt/pages.aspx?page=318

Prescribing Humour in Healthcare: and I ain't kiddin! Lectures at Mater Dei Hospital – log on http://www.thesynapse.net/events/view.asp?eventID=114

In 1996, the plan was clear. It is all proven by a carefully laid out brochure penned way back in preparation for the official launch which happened precisely on October 18th , 1996. The Synapse was in the pipeline, it happened and it's still going strong. Two great friends, Dr Gauden Galea and Dr Wilfred Galea most certainly had foresight when they mapped out what a successful medical professional's network should include.

Fast forward to 2010 and 14 years since its inception, The Synapse can happily tick off a great many of its original targets. Dr Wilfred Galea who has been at the steering wheel since 1998 says, "It is kind of strange to read what we wrote in this brochure in 1996. We certainly had foresight – that of fostering a community and a vision of creating a link between members of professional bodies, academics and corporate businesses. Internet was still in its swaddling clothes back then, but we were perceptive of its potential in facilitating communication."

The concept of providing a constantly updated, inexpensive and professional publication supported by the attention of a bevy of serious visitors and not merely casual passersby took off big time. And today, on the verge of launching a new look and feel to TheSynapse web portal, Wilfred is confident that the future holds even more potential in store.

"We currently supply daily updates on Maltese and international news from the medical world, details on upcoming conferences and fora, new books, locum posts, etc - it is in fact an efficient service designed specifically for busy people. We compliment this with the publication of The Synapse magazine and as always this is all openly and freely available to professionals from the medical field, specifically doctors, pharmacists, dentists and students of these professions."

Dr Galea, a busy family doctor as his main profession, has an effective team of similarly enthusiastic people working on this project. Whereas in 1996 it as a small, two person team, today, the team is made up of programmers, editors, scientific editors, marketing and administration staff – a fully fledged medical media company with a strong research and development focus and with a pipeline of planned innovations stretching for at least the coming two years. The Synapse today boasts of over 3000 members, 2000 of whom are Maltese. "The audience is actually very international with a wide range of countries passing through. I am constantly impressed by what some people manage to do online – even more so when connecting with people beyond our immediate European confines. People who interact through The Synapse are a boon to the system, helping to bring down barriers which are easily created through a quest for individualism."

And to answer the 'What's in it for users?' question , The Synapse not only supplies a wide range of important information, but also helps promote local and foreign medical-related events. "Our professionalism has also helped us clinch deals from huge companies for our members – all benefits that can be obtained when members use their MedClub Card"

Dr Galea continues, "We are launching a redesigned version of the portal and the emphasis will be on increased user interaction. Specifically we want to provide information on where members can share educational resources – this is particularly aimed at students from the first year of their undergraduate career to about 95 years post graduate! The aim is to allow members to upload and share useful material between them."

The Synapse - For further details contact editor@thesynapse.net or visit http://www.thesynapse.net

Focus on

Bacterial Vaginosis

What is its significance in cervical smear cytology reports?

A frequent bacterial vaginosis (BV) diagnosis, or suggested BV diagnosis, in cervical smear cytology reports is a relatively recent phenomenon, and is probably a source of confusion and concern to both doctors and their patients.

In the past, the same microscopic diagnosis used to be referred to as “clue cells”, and I wonder how many doctors understood the clinic significance of this pathological jargon. I have always been totally averse to pathology reports worded in jargon understandable only to pathologists rather than by the recipient of the surgical pathology report, namely, the clinician looking after the patient.

Diagnostic cytology was established and developed by cytologists with no experience of histopathology, and they invented their own nomenclature, often using Greek words, like koilocytosis and dyskaryosis, well before the underlying nature of the pathology was fully understood. Koilocytosis, for example, was coined in the 1950s and regarded as a type of dysplasia, almost 30 years before the causative Human Papilloma Virus (HPV) infection was established. At that stage, the distinction between HPV changes and Cervical Intraepithelial Neoplasia (CIN) was unknown. I personally see no point in using antiquated jargon instead of “HPV” and “CIN” nomenclature which is clearly understood by modern clinicians. The same applies, I feel, to complicated American cervical smear reporting nomenclature, which tries to sound cleverer than others, but actually achieves nothing better than simply using “HPV” and “CIN” diagnostic labels.

But let’s get back to BV. This was largely unrecognised by cervical smear reporters until relatively recently. Laboratory staff were also unaware of the connection between this microscopic diagnosis and possible clinical symptoms. As laboratories increasingly diagnosed, or suggested, the presence of BV, patients and some doctors have become concerned, both about the frequency of this diagnosis, and also about its clinical significance.

Of primary importance is reassuring patients that BV is not a sexually-transmitted disease (virgins may acquire it), although it is commoner in the sexually active. It is caused by an imbalance of naturally-occurring bacterial flora, whereby normal lactobacilli are partly or completely replaced by a variety of mainly anaerobic organisms, and vaginal discharge changes from acidic to alkaline.

BV is the commonest cause of abnormal discharge and up to 30% of women are thought to be affected. The prevalence in pregnant women is said to be even higher. The exact mechanisms of acquiring BV are not fully understood. Having a new sex partner, or multiple sex partners, and douching increase the risk. The mechanisms here might simply be too frequent exposure to alkaline seminal fluid, and the acidity diminishing effect of douching. Similarly, changes in hormonal status during the menstrual cycle, during the peri-menopause and menopause, and those caused by oral or intrauterine contraceptive hormones, would be expected to affect vaginal pH, and might be the triggering mechanism in these situations. In pregnancy, besides hormonal changes in the vaginal epithelium, subclinical iron deficiency anaemia might be another mechanism encouraging BV. Psychological stress has also been claimed to increase the risk.

The commonest symptom of BV is an abnormal homogenous thin whitish-grey vaginal discharge with an unpleasant fishy smell. However, most women report no signs or symptoms, while some do complain of dysuria and/or localised itching, pain and erythema., besides the foul discharge.

The possible complications of BV include increased susceptibility to sexually-transmitted infections (herpes, Chlamydia, gonorrhoea and HIV) and pelvic inflammatory disease with its possible long-term consequences (infertility and ectopic pregnancy), increased risk of infection following hysterectomy or abortion, and increased risk of preterm delivery.

But does cervical smear-reported BV require treatment? BV will sometimes clear up spontaneously, but all women with symptoms of BV should be treated to avoid complications. Male partners are said not to need treatment, but BV may spread between female sex partners.

Treatment is particularly important in pregnant women. A history of premature delivery or low birth weight should elicit an examination for BV. Some recommend treatment for BV in all women undergoing hysterectomy regardless of symptoms. Metronidazole or clindamycin are recommended for treating BV. Both can be used in non-pregnant women but caution should be exercised in pregnant ones. The recommended dosages differ in these two scenarios. BV may recur after treatment, and patients should be advised to take all the medicine prescribed even if the signs and symptoms abate.

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The Therapeutic Effects of Dead Sea Mineral-Based Skincare

By Allistair Mallia

Dead Sea mineral-based skincare can be considered a unique part of the 'Sea' cosmetic trend. The sea as a natural source of healing is quite an old concept.
In 1750 Richard Russell presented his thesis on the Therapeutic Effect of Seawater at Oxford. And in 1869 the term thalassotherapy, or "bringing together the sea and medicine" was coined by the French physician LaBonardier d'Arachon.
More than 40 different skincare brands based on Dead Sea minerals are sold worldwide. The success of Dead Sea products and theincreasing consumer expectations can be attributed to quantifiable consumer satisfaction surveys. These include mineral content, active and natural ingredients, doctor recommendations and their healing capabilities for healthier skin.
A cosmetic product as defined by European Council Directive 76/768/EEC, is "any substance or preparation intended for placing in contact with the various external parts of the human body… with the intention, exclusively or principally of cleaning perfuming or protecting to keep such parts in good condition, change their appearance or correct body odours." Skincare claims today have moved from the "care" claims originally envisaged by the Directive to "prevention", "protection" and even "healing" claims which are permitted. The 1997 "6th Amendment" however obliges cosmetic producers and marketors to scientifically prove their declared performance claims.[1]
The composition of Dead Sea minerals is unique. At a concentration of 32% (w/v) dissolved minerals, the Dead Sea is the richest natural mineral source in the world. The concentration of the divalent cations, magnesium and calcium is very high compared with the monovalent cations, mainly sodium and potassium. In addition, the ionic strength of the solution is very high. Upon application to skin, a concentration cascade is created with unique absorption kinetics characterized by a steep gradient into the multilayered bio-membrane, that is human skin. The hygroscopic properties of the minerals in turn, enhance intracellular water capacity and add water to the skin tissue from within. This explains the proven positive influence of Dead Sea mineral skincare on the skin's natural moisture content and its beneficial action on eczematous and atopic skin.[2]
Another common claim of Dead Sea mineral skincare relates to its smoothing effect on skin aged by environmental exposure and senescence. Blinded laser profilometric studies conducted by European dermatologic research institutes, in accordance with the ISO 4287/1, have confirmed that anti-wrinkle gels enriched with Dead Sea ingredient reduce wrinkle depth and skin roughness by more than 40% in female cohorts.[3]
The unique black hypersaline mud mined from the Dead Sea shores is extensively used in mud packs, masks and topical body and facial treatments in skincare preparations marketed worldwide. The mud has well-documented beneficial properties on, notably, psoriatic and acneic skin. In microbiological studies using conventional bacteriological media, high counts (up to 20,000 colonies per gram) of test microorganisms known to be skin pathogens (Escherichia coli, Staphylococcus aureus, Propionibacterium acnes, Candida albicans) rapidly lost their viability when added to plates treated with Dead Sea mud.[4] This mud also has protective anti-oxidant and anti-inflammatory properties that can antagonize biological the effects of UVB irradiation on skin. It may therefore be able to reduce skin photoaging, and more generally to reduce oxidative stress and inflammation in skin pathologies.[4]

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What is on for Health Promotion and Disease Prevention for September and October?

World Heart Day

Cardiovascular diseases are the world's largest killers, claiming 17.1 million lives a year. In Malta it is the top cause of mortality counting for 40% of all deaths. Risk factors for heart disease and stroke include raised blood pressure, cholesterol and glucose levels, smoking, inadequate intake of fruit and vegetables, being overweight, obesity, stress and physical inactivity.

26th September 2010 was World Heart Day and the Health Promotion and Disease Prevention Directorate's focus was on prevention of heart disease and early identification of risk factors.

To protect a healthy heart the key messages should be communicated to your patients:
1. Heart attacks and strokes are major – but preventable – killers worldwide.
2. Over 80% of cardiovascular disease deaths take place in low- and middle-income countries and occur almost equally in men and women. Cardiovascular risk of women is particularly high after menopause.
3. Tobacco use, an unhealthy diet, and physical inactivity increase the risk of heart attacks and strokes.
4. Cessation of tobacco use reduces the chance of a heart attack or stroke.
5. Engaging in physical activity for at least 30 minutes every day of the week will help prevent heart attacks and strokes.
6. Eating at least five servings of fruit and vegetables a day, and limiting your salt intake to less than one teaspoon a day, also helps to prevent heart attacks and strokes.
7. High blood pressure has no symptoms, but can cause a sudden stroke or heart attack. Have your blood pressure checked regularly.
8. Diabetes increases the risk of heart attacks and stroke. If you have diabetes control your blood pressure and blood sugar to minimize your risk.
9. Being overweight increases the risk of heart attacks and strokes. To maintain an ideal body weight, take regular physical activity and eat a healthy diet.
10. Heart attacks and strokes can strike suddenly and can be fatal if assistance is not sought immediately.
Source: WHO factsheet

Breast Cancer awareness

Breast cancer is among the malignancies where good opportunities for both primary and secondary prevention exist. Primary prevention here refers to promotion of healthy lifestyles, especially with regards to a diet that is rich in fruits and vegetables and low in saturated fats, whereas secondary prevention refers to early detection and treatment. October is pink to remind people of the importance of raising awareness on breast cancer. The directorate is currently launching a campaign with the collaboration of NGOs on breast cancer awareness. Focus will be made on self-examination at all ages, and referral to health professionals.

Professionals who would like a copy of the material are kindly asked to call on 23266000, email healthpro@gov.mt or visit http://www.sahha.gov.mt/pages.aspx?page=26. Alternatively one may also click on http://www.thesynapse.net/

Health Promotion Quizz

The Health Promotion and Disease Prevention Directorate is organising free weight management classes in health centres and aerobics in local councils for people who have BMI > _____ to encourage them to loose weight and stay healthy.

The answer can be found in Issue 3/10. The first drawn name will get a 3 month membership for a Parent and Kid at Spinach Fitness Club, Malta's first kids' gym – Melita Training Grounds, Pembroke. The gym may be contacted at www.spinachfitness.com or 21/79383740.

Kindly submit the answers by mail by filling the form on this page addressed to The Professional Services Centre, 3 Guzi Cutajar Street, Dingli, DGL 1201 or submit your answers on- line on www.thesynapse.net/quizz. All submissions will participate in a draw.
You have up to the 7th November 2010 to submit your answers

SPINACH FITNESS CLUB

Fill in your details

Name

Address

Email

Mobile

Splitting Of Erectile Dysfunction Pills

Pill splitting is the practice of splitting a pill in half, thus creating two pills, each aimed at being half the dose of the entire pill. This is typically done with a knife, using a pair of scissors, by hand or with a designated pill splitter. The main reason for pill splitting is a financial one. Pharmaco-economically speaking, a drug which is twice as strong as another may not be twice the price, in fact it may indeed be the same price. In order to make costs savings, patients choose to split a high-dose tablet to create two lower dose tablets.

What's the latest data on pill splitting?

In May 2009, Bayer surveyed 500 erectile dysfunction (ED) patients in five European countries (France, UK, Italy, Germany and Spain). The findings shed new light on the prevalence of and reasons for pill splitting1:

• 50% of those ED patients surveyed admitted to splitting their medication. This rose to 59% amongst high dosage users, which is more than every second patient;
o Of the total number who split their pills, 36% always split them and 40% split them every second time;
• Other reasons cited for pill splitting, over and above cost savings, were the belief that half the dosage is sufficient and that side-effects will be reduced, as well as concerns about too strong / lasting effects;
• Cutting with a knife was identified as the most popular way to split pills.

The implications of pill splitting

There is much debate amongst healthcare professionals and authorities regarding the implications, both positive and negative, of pill splitting. Although the cost-saving benefits are widely accepted, there are concerns about the impact on both patients and healthcare professionals. The US Food and Drug Administration (FDA) and the
American Medical Association for example, advise against pill splitting unless it's specified in the drug's labelling2. There are a number of reasons for this:
• Confusion over the correct dose. There have been cases when people have purchased higher strength tablets intending to split them, but then haven't, leading to patients accidently taking the wrong dose.

Equal distribution of medicine. FDA studies2 have shown that the actual dose in each half of a split tablet often is different. So while the two halves may look the same, they don't necessarily contain equal amounts of medicine. For the uniformity of mass of subdivided tablets a requirement has recently been set by the European Pharmacopoeia. Loss of mass upon breaking can be limited to not more than 1%.

• Difficulty splitting. Some tablets are too small to split, may have an unusual shape that makes them hard to split, or may crumble more easily when split.
From a healthcare professional's point of view, pill splitting means that they have limited control over the exact dose their patients take.

Bayer Cuts Price of its Erectile Dysfunction Drug Levitra®

Levitra® (vardenafil) is available in three different dosages - high (20mg), medium (10mg) and low (5mg) dose

Based on Individual Member State data, the most frequently prescribed dosage is the high one, but the most frequently taken is the medium dosage. This is because of pill splitting. ED treatment is different from many other therapy areas. It is a common, life-changing condition, yet there is no government reimbursement for treatment in most countries.

Because patients have to pay for ED treatment themselves, more than 50% of men with ED have been saving money by buying the high dose tablet and splitting it in half.

Bayer has therefore taken the decision to lower the price of Levitra® dramatically as a responsible course of action to meet men's needs – both therapeutic and economic - to help tackle this important ED treatment issue. Bayer has proactively reduced the price of its medium (10mg) and low (5mg) dose Levitra® (vardenafil HCL) in Malta so each dose is now approximately half the price of the next higher dose.

Now, patients who are currently splitting ED tablets such as Levitra® will have an option that specifically meets their dose requirements at significant savings, and doctors will have better control over the dose they prescribe.

In Malta, Levitra® is being sold at the revised prices with effect from 1st October 2010. The quality and efficacy of

	Previous Price per 4 tablet pack	New Price per 4 tablet pack
Levitra 5mg	EUR 36.19	**EUR 12.88**
Levitra 10mg	EUR 39.33	**EUR 24.02**
Levitra 20mg	EUR 44.72	**EUR 44.72**

Levitra® will not be compromised as a result of this price revision. Bayer Schering Pharma has consistent quality standards, which are checked periodically by local and regional health authorities. On the contrary, the reduced price of Levitra® removes economic hurdles for all ED patients who split pills and offers them greater convenience by removing the hassle to split pills, eliminating the possibility for wastage during splitting and lowering the financial outlay compared with competitor brands.

Levitra® is a proven ED medication which is well tolerated, and with a good safety profile in patients of all ages, with or without underlying medical conditions. It is the only PDE-5 inhibitor that extends duration of erection, as measured by a stopwatch method, up to 3 times over placebo.3 It is now available in pharmacies in Malta and Gozo at a new and more competitive price.

Reference
1. Market research: 'Pill Splitting Behaviour Among PDE V users' Conducted by PSYMA in May 2009 2. US Food and Drug Administration : Consumer Updates. July 2009 http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm171492.htm 3. Rosenberg MT et al. Improvement in duration of erection following phosphodiesterase type 5 inhibitor therapy with vardenafil in men with erectile dysfunction: the ENDURANCE study. Int J Clin Pract 2009; 63:1

Grape Expectations

Bordeaux & London

by Albert Cilia-Vincenti

"There is simply nothing else that so perfectly encapsulates physical sensation, social well-being and aesthetic exploration at the same time"

This is the second of a two part series on how the 18th and 19th century British middle classes shaped the wine industry

The wine trade flourished when Britain made peace with France in 1713. Claret was expensive, but rich Londoners (also big spenders on theatres and music produced by fashionable immigrants like Handel) consumed large quantities. Sir Robert Walpole, Britain's first prime minister, is said to have smuggled his favourite French wines in navy ships. The most expensive one he bought was old Burgundy, but that (as now) was only available in tiny quantities, so he relied largely on claret (Margaux and Lafite). In a single year his wine bill amounted to over £1,200 (£100,000 in today's money). British consumers bought the best stuff and paid top prices – they were paying five times as much for their claret as the wine's other main customers, the Dutch, who preferred the cheaper lower-grade stuff. Claret was no longer drunk, or even bought, when young. In 1714, Walpole bought classier bottles of the 1706 vintage. His sophistication was echoed by that of his clerk, who could spell correctly all four top First Growth estates.

Claret was still largely for the very well-off, well into the 19th century. In "Every Man His Own Butler", published in 1839, Cyrus Redding, a wine merchant and author, wrote "claret for a bishop, port for a rector, currant for a curate and gin for the clerk". At that time, for a tradesman, the fine-wine merchant was an unusually respectable figure. Anthony Trollope described one of them, "Mr Prettyman", as "a handsome old gentleman with grey hair, always well-dressed". Indeed, three of his contemporaries survive till this very day – Corney & Barrow in the City of London, Justerini & Brooks and Berry Bros & Rudd in St James's Street.

Claret was beginning to flow down the social hierarchy, and a free-trade treaty between Britain and France in 1860 drastically reduced duty on French wines, encouraging the British middle classes to ape their social superiors. Also that year, the British Chancellor of the Exchequer, William Gladstone, keen to stiffen the nation's moral spine, cut the duty on table wine to 40% of that on the more intoxicating fortified wines such as port and sherry. The year after came the Single Bottle Act, allowing grocers to sell wine by the bottle. A much-despised, enormously popular drink called "grocers' claret" emerged, resulting in sales of cheap Bordeaux wine to rise six-fold to 36 million bottles between 1859 and 1878. The Gilbey family franchised 2,000 grocers licensed to sell wine, largely claret, and became one of the most remarkable commercial dynasties of Victorian England.

As the middle classes turned to claret, the upper classes abandoned this increasingly common tipple in favour of Hock (German white wine made from Riesling grapes) and Champagne. Because fashion determines price, the records of wine merchants Berry Bros & Rudd reveal that the price, a hundred years ago, of top Hock wines exceeded that of top Bordeaux reds, Margaux and Latour of same vintage ... unbelievable today.

The fortunes of the claret business turned in the late 1870s and 1880s when mildew tainted and ruined the wines. Lafite's reputation, for instance, went downhill when the 1884 vintage turned mouldy after only a couple of years in bottle. At the same time, the phylloxera virus started devastating Bordeaux's vineyards.

Claret recovered in 1960 when the splendid 1959 vintage coincided with the arrival of big American buyers, and its popularity has risen steadily since. London remains at the centre of the fine wine trade, and home of organisations such as the Institute of Masters of Wine, of Decanter and World of Fine Wine magazines, and most of the world's biggest wine auctions. Liv-Ex, the world's first fine wine stock-market, is based in London, and its records show that nine-tenths of the wine trade is still in top ("classed growths") clarets. Newcomers from vineyards in a dozen countries trying to launch their finest wines on the world market come to London first for validation. Yet, though London may still have much knowledge as well as the market, the British, as customers, may be past their best. More than half of fine wine sold globally, by value, is now bought by Asians, most of which are from China and Hong Kong. No wonder therefore that fifteen years ago Berry Bros & Rudd, the three hundred year-old London wine merchant, opened a shop in Hong Kong.

As wealth has shifted from Europe and America to China, First Growth clarets have become one of the status symbols of Asian multimillionaires. Inevitably anything that is scarce and fashionable is bound to become very expensive, and these very top clarets are now out of reach of average wine-lovers' pockets. However, there is no proportionality between price paid and gustatory pleasure offered, and a €1,000 wine will not provide twenty times the aromatic and flavour excitement offered by a €50 one. However whether wine-label romantics like it or not, there is definitely a quality-price ratio for practically anything on earth. The blind-tasting format of our "Il-Qatra" wine club is based on this principle, educating members that when you haven't been influenced by the sight of the bottle labels, you might well prefer a cheaper wine to a more expensive one.

Breast Cancer: Ductal Carcinoma in situ (DCIS)

by Pierre Vassallo

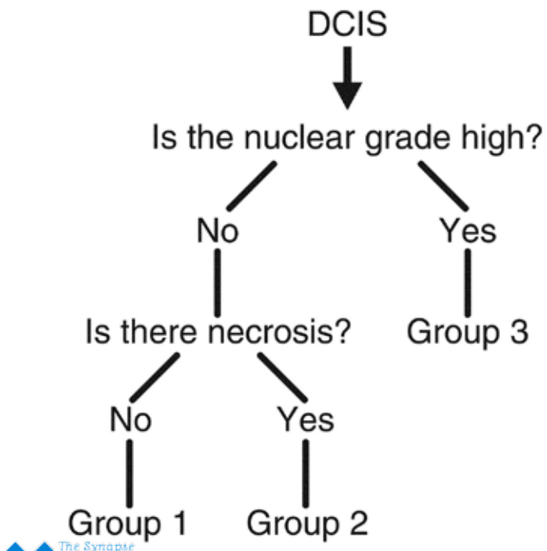
Ductal carcinoma in situ (DCIS) is a breast malignancy that is characterized by the proliferation of malignant ductal epithelial cells without evidence of invasion through the basement membrane. The incidence of DCIS has risen 11-fold between 1981 and 2001 through improved detection rates with screening mammography.

DCIS is not a single entity but a spectrum of disease ranging from low to high grade. DCIS grade is an important prognostic factor with high grade lesions being more likely to recur.

The simplest, most reproducible classification system of DCIS is the Van Nuys system, which identifies three groups of DCIS lesions. In the Van Nuys system, lesions are differentiated first according to nuclear grade (high, intermediate or low grade) and then according to whether necrosis is present or absent. Low-grade lesions contain cells with small nuclei, minimal nuclear pleomorphism, and infrequent mitoses, whereas high-grade lesions have cells with large, pleomorphic nuclei and frequent mitoses. Intermediate-grade lesions contain cells with nuclei that are neither low nor high grade. Figure 1 shows the Van Nuys system for classification of DCIS: First, lesions are classified according to whether they are of a high nuclear grade (group 3) or not. Non–high-grade lesions are further differentiated according to whether necrosis is present (group 2) or absent (group 1).

Mammography is the primary tool for detecting DCIS, but it has limitations. The reported sensitivity of mammography for detection of DCIS is between 87% and 95%. Mammography is more reliable in detecting higher grade lesions, while ultrasound was more useful than mammography for lower grade DCIS.
The most common mammographic finding in DCIS is

Figure 1. Van Nuys Classification



microcalcifications. Microcalcifications tend to correlate with intraductal foci of necrosis. Thus a low-grade lesion without necrosis is less likely to manifest with calcifications than either an intermediate- or a high-grade lesion. Other mammographic findings might include a mass (Figure 2) or architectural distortion (Figure 3) and may be present in any grade lesion. The mass lesion in DCIS may directly correlate with tumor tissue, but may also be the result of periductal fibrosis or elastosis.

The most typical calcifications in DCIS are linear with or without branching (following the ducts) (Figure 4). Fragmentation of the calcifications is also indicative of malignancy, while rounded calcifications if abundant (>5 calcifications within an area 1cm in diameter) may also suggest DCIS (Figure 5).

Magnetic resonance (MR) imaging has higher sensitivity than mammography for the detection of DCIS and greater accuracy for depicting the extent of disease. However fibrocystic change may be indistinguishable and this leads to a poor specificity and also a limited usefulness of MRI for pre-operative planning. The MR appearance of DCIS depends primarily on the presence and extent of abnormal vascularity (tumor angiogenesis) resulting in the presence of

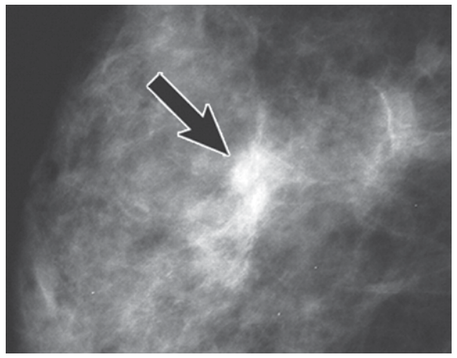


Figure 2. Mass lesion (arrow) in DCIS Grade 1

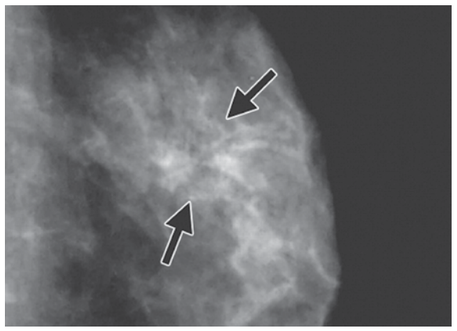


Figure 3. Architectural distortion (arrow) in DCIS Grade 1

abundant and leaky vessels. Therefore contrast-enhanced T1 weighted images are required that are obtained preferably as a 3D acquisition with high spatial resolution in a sequentially repeated fashion in order to observe both the degree and distribution of contrast agent uptake and the temporal the pattern of enhancement.

Non-mass-like (not nodule-shaped) enhancement typically involving a segment of the breast with some clumping is

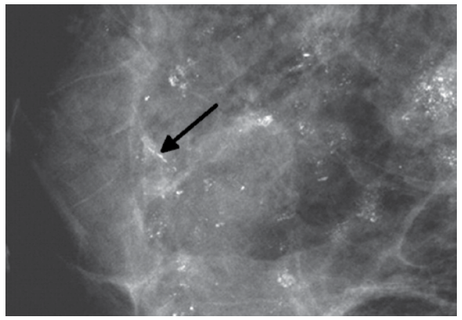


Figure 4. Linear calcifications in DCIS Grade 3

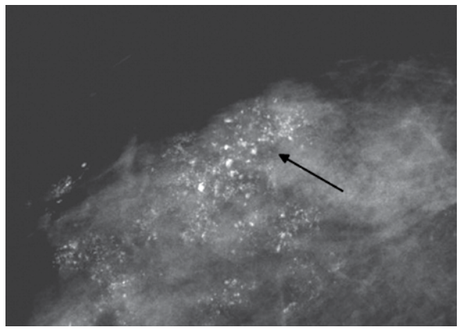


Figure 5. Abundant rounded microcalcification in DCIS Grade 2

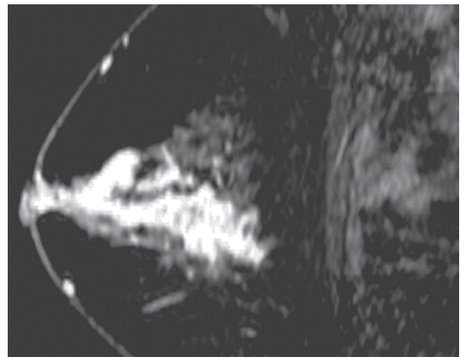


Figure 6. Segmental enhancement on MRI in DCIS Grade 3

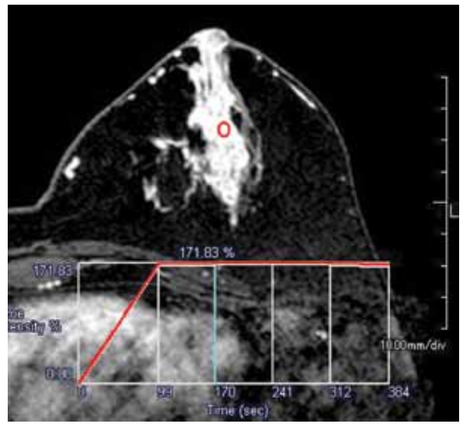


Figure 7. Kinetic analysis of contrast material uptake on MRI in Grade 3 DCIS: graph plotting degree of enhancement vs time shows rapid initial uptake and a prolonged plateau of enhancement

suggestive of DCIS (Figure 6). The kinetic pattern of contrast enhancement is more related to histologic grade with low grade lesions showing rapid uptake and loss of contrast material during the later phases (washout), whilst higher grade lesions tend to have slower uptake patterns with a prolonged plateau enhancement (Figure 7). Speed of contrast material uptake is related to vessel abundance, while the degree of prolongation of uptake (length of plateau phase) is a function of vessel permeability (leakiness).

The reported sensitivity of CT for the detection of DCIS ranges from 70% to 88%. In a different study, the detectability of the intraductal component of invasive ductal carcinomas at multidetector CT was compared with that at MR imaging; lesion detectability at multidetector CT was inferior to that at MR imaging. In general, CT has lower sensitivity but higher specificity than MR imaging because the lesion appearance leads to overestimation of fibrocystic changes at MR imaging. Multidetector CT may be used to map lesions for breast-conserving surgery, however presurgical mapping has been shown to be more helpful in invasive ductal cancers than for DCIS.

In summary, the incidence of DCIS has increased dramatically due to increased detection with screening mammography. The definitive correlation of histologic grading of DCIS (Van Nuys Classification) with mammographic findings and the use of MRI particularly in equivocal cases confirms the validity of both investigations, which can therefore strongly contribute to improved patient outcome.

Help Protect Your Patients From Osteoporotic Fractures

NEW With 5,600 IU of Vitamin D!

FOSAVANCE™

alendronate/colecalciferol

The Only Osteoporosis Therapy That Provides

- **Demonstrated Fracture Prevention at the Hip and Spine Plus 5,600 IU of Vitamin D**
- **In a Single, Once-Weekly Tablet**

Actual size

FOSAVANCE™ is indicated for treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency. FOSAVANCE reduces the risk of vertebral and hip fractures.[1]

FOSAMAX™ and FOSAVANCE are contraindicated in patients with esophageal abnormalities which delay esophageal emptying (eg, stricture or achalasia) and in patients unable to stand or sit upright for at least 30 minutes. FOSAMAX and FOSAVANCE are contraindicated in patients with hypocalcemia (see WARNINGS AND PRECAUTIONS) and in patients with hypersensitivity to any component of these products. Hypersensitivity reactions including urticaria and angioedema have been reported. FOSAMAX and FOSAVANCE, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.[1]

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping treatment.[1]

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates.[1]

NOF = National Osteoporosis Foundation.

References

1. Worldwide Product Circular for FOSAVANCE, 2007.
2. NOF Scientific Statement. National Osteoporosis Foundation's Updated Recommendations for Calcium and Vitamin D$_3$ Intake. Revised. www.nof.org/prevention/calcium_and_Vitamin D.htm. Accessed 30 July 2009.

Before prescribing, please read the full Prescribing Information on the adjacent page.

Updated NOF guidelines recommend 800–1,000 IU of vitamin D per day for adults ≥50 years[2]

FOSAVANCE 5600 retail price (Pack of 4) € 37.55

MSD MUSCULOSKELETAL

7-11 FSP-2007-W-1224165-i
31-Jul-2011 FSP-2010-MEA-1982-i

1. NAME OF THE MEDICINAL PRODUCT

FOSAVANCE™ 70 mg/5600 IU tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D_3).

Excipients:
Each tablet contains 43 mg lactose anhydrous and 16 mg sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Modified rectangle-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and '270' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency. FOSAVANCE reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

The recommended dosage is one FOSAVANCE tablet once weekly.
Due to the nature of the disease process in osteoporosis, FOSAVANCE is intended for long-term use.

To permit adequate absorption of alendronate:
FOSAVANCE must be taken with water only (still mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

The following instructions should be followed exactly in order to minimise the risk of oesophageal irritation and related adverse reactions (see section 4.4):
FOSAVANCE should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml or 7 fl oz).
Patients should only swallow FOSAVANCE whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
Patients should not lie down for at least 30 minutes after taking FOSAVANCE.
FOSAVANCE should not be taken at bedtime or before arising for the day.
Patients should receive supplemental calcium if intake from diet is inadequate (see section 4.4). The equivalence of 1 tablet of 5600 IU of vitamin D_3 weekly to FOSAVANCE to daily dosing of vitamin D 800 IU has not been studied.

Use in the elderly:
In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

Use in renal impairment:
No dosage adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min. FOSAVANCE is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children and adolescents:
FOSAVANCE has not been studied in children and adolescents and therefore should not be given to them.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
Inability to stand or sit upright for at least 30 minutes.
Hypocalcaemia.

4.4 Special warnings and precautions for use

Alendronate:
Alendronate can cause local irritation of the upper gastrointestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease (such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty) (see section 4.3).
In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate as an individual patient basis.
Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain or new or worsening heartburn (see section 4.8).
The risk of severe oesophageal adverse reactions appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and are understood by the patient (see section 4.2). Patients should be informed that failure to follow those instructions may increase their risk of oesophageal problems.
While an increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and with complications (see section 4.8).
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer who are receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.
A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, periodontal disease).
While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.
Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.
Stress fractures (also known as insufficiency fractures of the proximal femoral shaft) have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit/risk assessment.
Patients should be instructed that if they miss a dose of FOSAVANCE they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.
FOSAVANCE is not recommended for patients with renal impairment where GFR is less than 35 ml/min (see section 4.2).
Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.
Hypocalcaemia must be corrected before initiating therapy with FOSAVANCE (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting FOSAVANCE. The content of vitamin D in FOSAVANCE is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with FOSAVANCE.
Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption) (see section 4.8).

Colecalciferol:
Vitamin D_3 may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated production of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.
Patients with malabsorption may not adequately absorb vitamin D_3.

Excipients:
This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Alendronate:
If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see sections 4.2 and 5.2).
No other clinically significant interactions with medicinal products are anticipated. A number of patients in the clinical trials received oestrogen (ethinylestradiol, trioxifene), or oral/ iv/im taking alendronate. No adverse reactions attributable to their concomitant use were identified.
Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.
Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of interactions of clinical relevance.

Colecalciferol:
Diuretics, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine and thiazides may increase the catabolism of vitamin D. Additional vitamin D supplements may be considered on an individual basis.

4.6 Pregnancy and lactation

FOSAVANCE is only indicated for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.
There are no adequate data from the use of FOSAVANCE in pregnant women. Animal studies with alendronate do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3).
It is not known whether alendronate is excreted into human breast milk. Colecalciferol and some of its active metabolites pass into breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
However, certain adverse reactions that have been reported with FOSAVANCE may affect some patients' ability to drive or operate machinery. Individual responses to FOSAVANCE may vary (see section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported during clinical studies and/or post-marketing use with alendronate.
No additional adverse reactions have been identified for FOSAVANCE.
[Common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000)]

Nervous system disorders: *Common:* headache. ***Eye disorders:*** *Rare:* uveitis, scleritis, episcleritis. ***Gastrointestinal disorders:*** *Common:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
Uncommon: nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena
Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal perforations, perforation, ulcers, bowel/jejunal stenosis* (see section 4.4). *See sections 4.2 and 4.4

Skin and subcutaneous tissue disorders: *Uncommon:* rash, pruritus, erythema, rare: rash with photosensitivity
Very rare: severe skin reactions including Stevens- Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders: *Common:* musculoskeletal (bone, muscle or joint) pain
Rare: severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)
Metabolism and nutrition disorders: *Rare:* symptomatic hypocalcaemia, often in association with predisposing conditions, (see section 4.4)
General disorders and administration site conditions: *Rare:* transient symptoms as in an acute phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.
Immune system disorders: *Rare:* hypersensitivity reactions including urticaria and angioedema

During post marketing experience the following reactions have been reported (frequency not known):
Nervous system disorders: dizziness, dysgeusia
Ear and labyrinth disorders: Vertigo
Skin and subcutaneous tissue disorders: Alopecia
Musculoskeletal, connective tissue and bone disorders: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4); joint swelling; stress fractures of the proximal femoral shaft (see section 4.4)
General disorders and administration site conditions: asthenia, peripheral oedema

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 % and 10 %, respectively, of patients taking alendronate 10 mg/day versus approximately 12 % and 3 % of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

4.9 Overdose

Alendronate:
Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse reactions, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdose.
No specific information is available on the treatment of overdose with alendronate. In case of overdose with FOSAVANCE, milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Colecalciferol:
Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults a 4,000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, combinations. ATC code: M05BB03.
FOSAVANCE is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D_3).

Alendronate
Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Colecalciferol (vitamin D_3)
Vitamin D_3 is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D_3 by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 is converted to 25-hydroxyvitamin D_3 in the liver, and stored until needed.
Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is tightly regulated. The principal action of 1,25 dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.
Vitamin D_3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphatemia, proximal muscle weakness and osteomalacia. further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.
Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations (SD) below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

FOSAVANCE studies
The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2800 IU) on vitamin D status was demonstrated in a 15-week, multinational study that enrolled 682 osteoporotic post-menopausal women (serum 25-hydroxyvitamin D at baseline, mean, 58 nmol/l (22.3 ng/ml), range, 22.5-225 nmol/l [9.00 ng/ml]). Patients received the lower strength (70 mg/2800 IU) of FOSAVANCE (n=336) or FOSAMAX (alendronate) 70 mg (n=332) once a week, additional vitamin D supplements were prohibited. After 15 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher (26 %) in the FOSAVANCE (70 mg/2800 IU) group (66 nmol/l [23 ng/ml]) than in the alendronate-only group (49 nmol/l [18.2 ng/ml]). The percentage of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D < 37.5 nmol/l [< 15 ng/ml]) was significantly reduced by 62.5 % with FOSAVANCE (70 mg/2800 IU) vs. alendronate-only (12 % vs. 32 %, respectively), through week 15. The percentage of patients with vitamin D deficiency (serum 25-hydroxyvitamin D < 22.5 nmol/l [< 9 ng/ml]) was significantly reduced by 92 % with FOSAVANCE (70 mg/2800 IU) vs. alendronate-only (1 % vs 13 %, respectively). In this study, mean 25-vitamin D, 22.5 to 37.5 nmol/l [9 to < 15 ng/ml]) increased from 30 nmol/l (12.1 ng/ml) to 49 nmol/l (15.6 ng/ml) at week 15 in the FOSAVANCE (70 mg/2800 IU) group (n=275) and decreased from 32 nmol/l (12.6 ng/ml) at baseline to 26 nmol/l (10.4 ng/ml) at week 15 in the alendronate-only group (n=270). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.
The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2800 IU) plus an additional 2800 IU Vitamin D_3 for a total of 5600 IU (the amount of vitamin D_3 in the higher dose of FOSAVANCE) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin D_3 5600 group received FOSAVANCE (70 mg/2800 IU) (n=296) and patients in the Vitamin D_3 2800 group received FOSAVANCE (70 mg/2800 IU) plus an additional 2800 IU vitamin D_3 (n=309) once a week; additional vitamin D supplements were allowed. After 24 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher in the Vitamin D_3 5600 group (93 nmol/l [37.6 ng/ml]) than in the Vitamin D_3 2800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 0.4 % in the Vitamin D_3 2800 group vs. 3.2 % in the Vitamin D_3 5600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin D_3 2800 group vs. zero in the Vitamin D_3 5600 group. There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups. The percentage of patients with hypercalciuria at the end of the 24-week extension was not statistically different between treatment groups.

Alendronate studies:
The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1 % (95 % CI: 4.8, 5.4 %) in the 70 mg once-weekly group and 5.4 % (95 % CI: 5.0, 5.8 %) in the 10 mg daily group. The mean BMD increases were 2.3 % and 2.9 % at the femoral neck and 2.9 % and 3.1 % at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.
The effects of alendronate on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT n=6,459).
In the initial efficacy studies, the mean BMD increases with alendronate 10 mg/day relative to placebo at three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48 % reduction (alendronate 3.7 % vs placebo 6.2 %) in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies (668) at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.
FIT consisted of two placebo-controlled studies using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):
FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (crush-related) fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47 % (alendronate 7.9 % vs. placebo 15.0 %). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1 % vs. 2.2 %, a reduction of 51 %).
FIT 2: A four year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37 % of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0 % vs placebo 2.2 %, a reduction of 56 %) and in the incidence of ≥ 1 vertebral fracture (2.9 % vs. 5.8 %, a reduction of 50 %).

5.2 Pharmacokinetic properties

Alendronate

Absorption
Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly in an estimated 0.40 % and 0.39 % when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.
The alendronate component in the FOSAVANCE (70 mg/5600 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.
Bioavailability was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60 %.
In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 26 % to 44 %).

Distribution
Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of alendronate in plasma following therapeutic oral doses are too low for analytical detection (< 5 ng/ml). Protein-binding in human plasma is approximately 78 %.

Biotransformation
There is no evidence that alendronate is metabolised in animals or humans.

Elimination
Following a single intravenous dose of [^{14}C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95 % within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Colecalciferol
Absorption
In healthy adult subjects (males and females), following administration of FOSAVANCE 70 mg/5600 IU after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}6d\ (trial)}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3) levels was 480.2 ng·h/ml. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 12.2 ng/ml and the median time to maximal serum concentration (t_{max}) was 10.6 hours. The bioavailability of the 5600 IU vitamin D_3 in FOSAVANCE is similar to 5600 IU vitamin D_3 administered alone.

Distribution
Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Biotransformation
Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form.
Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Elimination
When radioactive vitamin D_3 was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4 %, and the mean faecal excretion of radioactivity after 4 days was 4.9 %. In both cases, the excreted radioactivity was almost exclusively an metabolite of the parent. The mean half-life of vitamin D_3 in the serum following an oral dose of FOSAVANCE (70 mg/2800 IU) is approximately 24 hours.

Characteristics in patients
Preclinical studies show that alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data

Non-clinical studies with the combination of alendronate and colecalciferol have not been conducted.

Alendronate
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia. In dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

Colecalciferol
At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Lactose anhydrous
Medium chain triglycerides
Gelatin
Croscarmellose sodium
Sucrose
Colloidal silicon dioxide
Magnesium stearate (E572)
Butyl hydroxytoluene (E321)
Modified starch (maize)
Sodium aluminium silicate (E554)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in the original blister to order to protect from moisture and light.

6.5 Nature and contents of container

Blister with paired aluminium/aluminium blisters, in cartons containing 2 (1 wallet x 2 tablets), 4 (1 wallet x 4 tablets), 12 (3 wallets x 4 tablets) or 40 (10 wallets x 4 tablets) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER(S)

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/310/008 - 2 tablets
EU/1/05/310/007 - 4 tablets
EU/1/05/310/006 - 12 tablets
EU/1/05/310/009 - 40 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

24 August 2005

10. DATE OF REVISION OF THE TEXT

09 November 2009

Healing & Disease Reversal The Series

by Albert Cilia-Vincenti

This series explores Dean Ornish's 30-year research experience into healing & disease reversal by dietary and lifestyle changes. He is a Californian University Professor of Medicine in San Francisco.

The good news, according to Dean Ornish, is that it's not difficult to eat and live in a healthy way. These articles, summarising his programme, amount to a scientifically proven field guide to help distinguish fact from fiction, hype from hope.

Ornish says he never intended becoming a veteran of diet wars. He has been forced into debating the late Dr Atkins at scientific meetings of the American Heart Association, the American College of Cardiology, and the American Dietetic Association, where he usually found himself described as the "low fat" doctor and Dr Atkins the "low carb" doctor. He insists that was not accurate, because he has always advocated that an optimal diet is low in total fat, very low in "bad fats" (saturated fat, hydrogenated fats, trans-fatty acids), high in "good carbs" (fruits, vegetables, whole grains, legumes and soy products), low in "bad carbs" (sugar, white flour), and that has enough of the "good fats" (omega-3 fatty acids) and high-quality proteins.

We need practical, clear, scientifically based information and not controversies between experts. Many people feel more bewildered than ever when they hear seemingly contradictory advice about different diets, and in fact a convergence of recommendations is evolving. Some significant differences remain, but a greater consensus is emerging among nutrition experts.

The first rule in Ornish's programme is to consume some omega-3 fatty acids every day. Omega-3 fatty acids are found in cold-water fatty fish (salmon, mackerel, herring, trout, sardines, albacore tuna), as well as canola (rapeseed), soy-bean, flaxseed and walnut oils. (in contrast, olive oil does not contain much omega-3 fatty acids). They are also present in smaller concentrations in dark green leafy vegetables such as kale and collard greens.

Omega-3 fatty acids reduce blood triglycerides, lower blood pressure, and decrease inflammation (hence reducing symptoms of arthritis, dermatitis and other inflammatory diseases as well as autoimmune diseases such as lupus). They reduce inflammation in blood vessels walls and prevent blood clots, thus decreasing the risk of heart attack and stroke. They also help prevent irregular heartbeats such as atrial fibrillation, another potential cause of stroke. Studies have in fact shown a potential reduction of risk of sudden cardiac death by 40-90% by stabilising the heart rhythm; the American Heart Association recommends at least two servings of cold-water fatty fish per week.1,2

Other benefits are claimed for omega-3 fatty acids. They are important components of all our cell membranes, including neurons and, when given to pregnant and lactating women, they increase IQ and reduce incidence of allergy in the offspring, and also reduce the risk of maternal postpartum depression.3 They also decrease the risk of dementia, improve immunity and reduce the risk of prostate, breast and colon cancer.

In non-breast-fed babies, omega-3 fatty acids-enriched feeding formulas have been shown to increase intelligence test scores by up to seven points. A study published in The Lancet stated that children of mothers who consumed more than 340 grams per week of omega-3 fatty acids-rich seafood had higher IQs, better behaviour, fewer problems with their peers, less hyperactivity, fewer emotional disorders and better communications skills than those mothers who consumed less or no seafood.4

Ornish says he's been taking fish oil capsules (3g daily) for many years and advises practically everyone to do the same. It is advisable to take a high quality fish oil (not cod liver oil) which has been purified of all possible fish pollutants, such as mercury, dioxin and PBCs. This gives all the benefits of omega-3 fatty acids without the extra fat, calories and pollutants that come with eating fish.

Are omega-3 fatty acids universally beneficial? There are conflicting reports about their usefulness in heart failure, some claiming benefit and others a dangerously negative effect, so caution would need to be exercised in this serious situation. For most people, omega-3 fatty acids are highly beneficial.

Can you consume too many good fats? One of the few remaining differences in the consensus of what constitutes an optimal diet has to do with how much "good fat" to include in your diet. Is olive oil the healthiest fat? In a word, no – it's a better fat but not the best one. The Harvard School of Public Health, and some authors of popular books, have promoted the idea that it doesn't matter how much fat you consume as long as it's "good fats", such as olive oil. While good fats are better than bad fats, the total amount of fat in your diet also plays an important role. Oils are 100 per cent fat, and because fat has more than twice the calories per gram compared to those of protein and carbohydrates, it's very easy to consume a lot of extra calories if you have a lot of fat. So remember … dipping bread in olive oil and pouring it on salads does increase substantially your calorific consumption!

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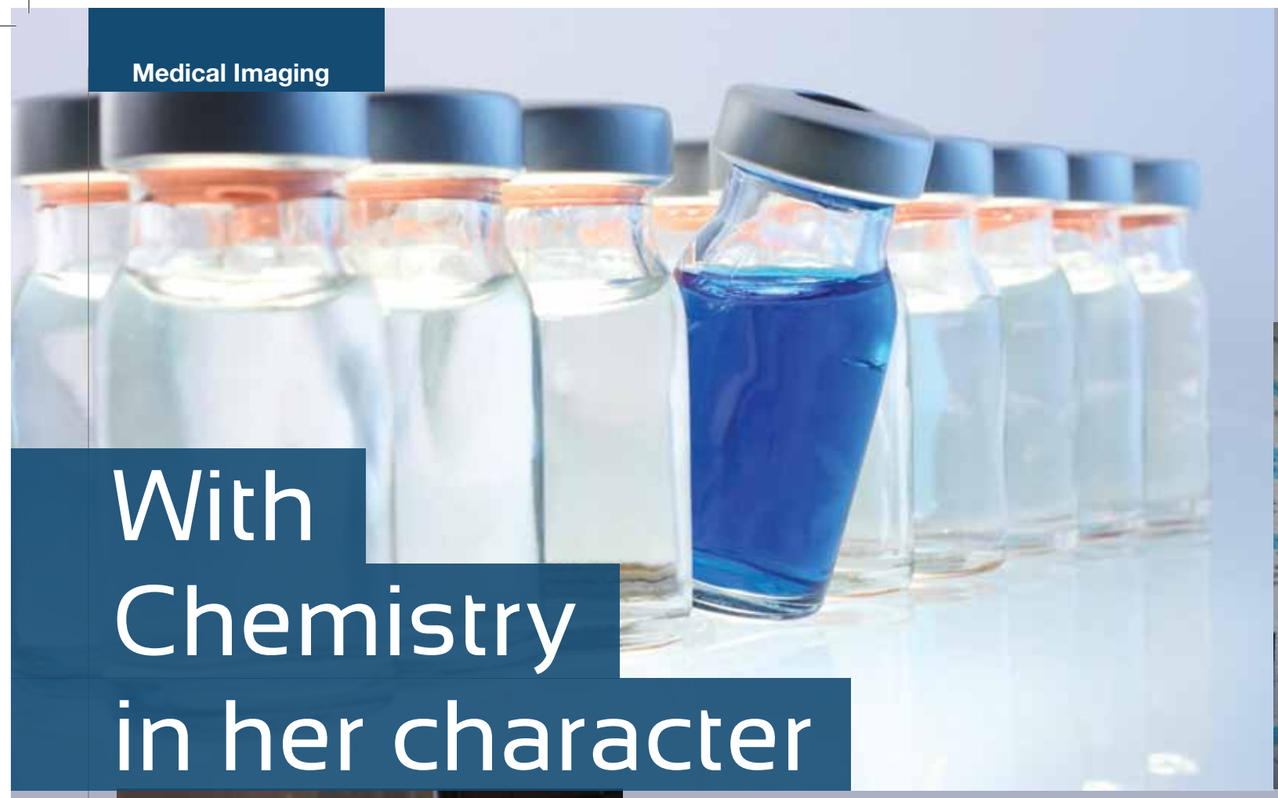

With Chemistry in her character

When Alison Anastasi started studying to become a pharmacist, little did she know she'd become one through and through. Seven years down the line, she is today Principal Pharmacist at the Directorate of Pharmaceutical Policy and Monitoring (DPPM) at St Luke's Hospital, and has been in this post for the past year. We meet at her office in a building which is surprisingly neat and well-organised…. But then what would one expect of a place housing professional pharmacists intent on monitoring the profession? Alison is herself very disciplined in what she does and the simple fact that she holds such an important post at the relatively young age of 30 is significant. Starting from a first post at the Extemporaneous and Chemotherapy Section in St Luke's Hospital, she was thrown in at the deep end. "My work was in compounding specialised medication for very special patients, mostly paediatrics. For me, at such a young age, being given the responsibility of preparing medicine for children in a situation where their health was so precarious….. well, let's say it was an extremely sobering experience. It made me fully aware of the great responsibility shouldered by a pharmacist. It's not simply about picking bottles off a shelf."

Her next experience was in the Out-Patients and In-Patients Department when she went into Formulary Management, taking care to keep a balance in stocks of medication, dealing with shortages and the general running of the biggest pharmacy on the Islands. Alison speaks somewhat fondly of this experience because she knows fully well that if one learns to manage such a fluid pharmacy, one can manage any pharmacy. Then came the migration to Mater Dei Hospital.

"The migration was another big task which landed on my lap and which taught me a great deal. Admittedly, I am always seeking new ways of enlarging my expertise where pharmacy and pharmaceutical supplies are involved. I got the opportunity of training in Disaster Preparedness which helped me in learning to work in collaboration with the Emergency Department. It wasn't and isn't something I do for the money because in most instances it is something done on a voluntary basis. I volunteered at the huge public events such as Isle of MTV and was also involved in the 2005 CHOGM. It is the kind of work which allows me as a pharmacist to work in collaboration with doctors, advising on the best medication to take 'on the field' so to say."

Today, she admits she misses that direct contact with doctors, with medics, with staff on the ward rounds and with patients. Her role as Principal Pharmacist is mostly administrative but she keeps tabs on the hands-on

part of the profession by doing regular locum hours in community pharmacies. Alison amazes me further when she flippantly mentions that since her graduation, and in her free time, she has also managed to cram in a course in Nutrition and Dietetics which she completed successfully and also got a Masters in Pharmacy. And she is actually in her first year of studies for a PhD in Pharmacy, delving into the research of a very specific topic – Pharmaceutical Case Models in Heart Failure. Her work at the DPPM is pretty intense and involves responsibilities linked to all Government and Health Centre pharmacies. The DPPM is responsible for the Medicines Entitlement Unit; the inclusion of new drugs on the government formulary; ongoing formulary maintenance; the Pricing Unit; the management of exceptional and urgent treatment cases and the participation within EU international foras. Being also involved in the Pharmacy Council as one of the elected members, Alison is serious about raising awareness on the general needs and obligations of pharmacists. She looks forward to work with the other council members to ensure that pharmacists in Malta continue to perform to the highest standards to protect and promote public wellbeing, thus, keeping a well-regulated dynamic profession.

"From my experience in teaching pharmacy students at the University of Malta, I find that the numbers of new recruits in our profession is increasing every year. There are more female than male pharmacists, so we face the usual employment issues that can greatly hamper manpower – you know, pharmacists get pregnant too! Having said that, females still outnumber male pharmacists." Asked about what she thinks of the present state of the profession, Alison points out, "Some pharmacists appear to be deeply rooted in the traditional approach, mainly to the distributive practice model. To ensure a high-quality advanced practice, pharmacists need to come in line and identify more with modern practices, such as pharmaceutical care and drug information."

She also tackles the hot issue of pharmacist prescribing. "In other countries this practice has been going on for years. Pharmacists possess a wealth of knowledge on medicine so I believe that collaboration between doctors and pharmacists will work in favour of the patient whom both professions have at heart – priority is our patients!"

As a sideline, Alison speaks of her passion for travelling which helps her unwind and put aside real life issues associated to illnesses, It can become overwhelming to say the least, and whilst reading and watching films remain her two strongest favourite pastimes, she admits she prefers to read or watch fiction rather than true-life stories. "I have to deal with enough drama as it is. When I unwind, it has to be really and truly to try and get a good laugh every so often. There is more to life than just playing chemist."

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1. The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572. **2.** The GUIDE Study. *Eur J Clin Invest.* 2004;34:535-542. **3.** The STENO 2 Group Study. *N Engl J Med.* 2008;358:580-591. **4.** The CONTROL Study. *Diabetologia.* 2009;52:2288-2298. **5.** Khalangot M, Tronko M, Kravchenko V et al. *Diabetes Res Clin Pract.* 2009;20(6):611-615. **6.** Diamicron MR 60 mg. *Product Monograph.* **7.** Drouin P. and the Diamicron MR Study Group. *J Diabetes Complications.* 2000;14:185-191. **8.** Sawada F, Inoguchi T, Tsubouchi H, et al. *Metabolism.* 2008;57(8):1038–1045. **9.** Del Guerra S, D'Aleo V, Lupi R, et al. *Diabetes Metab.* 2009;35(4):293-298. **10.** Katakami N, Yamasaki Y, Hayaishi-Okano R, et al. *Diabetologia.* 2004;47:1906-1913.

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