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Food Supplements:
What are they and how ro report adverse reactions?

Quick Read
Food supplements are not medicinal products, though they are marketed in dosed forms including capsules, tablets, sachets, etc. It is not always obvious how to report suspected adverse reactions to food supplements.

Food supplements have specific characteristics such as their presentation in dosed forms. They are concentrated sources of nutrients or other substances with nutritional or physiological effects, given as single or combination ingredients. They are supposed to complement or supplement a normal feeding regime and must not be used as replacement for a diversified diet.

Food supplements should have a beneficial effect but they are not medicines. As such they may not be presented as having preventive, therapeutic or healing properties for diseases or their symptoms. Labelling, presentation and advertising may not mention those properties either. Marketing of these products should comply with Portugal Law Decree 136/2003, which transposes **EU Directive 2002/46/CE**.

Within the European Union it is for each member state, in accordance with applicable national law, to decide whether a product is to be construed as a food supplement or as a medicinal product – this may vary across countries.

Categories used for food supplements are not always clear and some overlapping may occur. They can be divided into **three broad groups**: vitamins and minerals, plants and herbal extracts, and other ingredients (see table overleaf). According to one Portuguese study, plants/extracts (56%) and vitamins/minerals (23%) are the most prevalent ingredients on national food supplement market labels.[1]

There is moreover a **category of borderline products** which are ingredients that may be simultaneously defined as medicinal products and food supplements. Food legislation does not preclude ingredients with pharmacological activity to be included in the composition of food supplements. This means that the same ingredient may be marketed under diverse requirements (food legislation or medicines legislation). The following are examples of ingredients included in borderline products: glucosamine/chondroitin, melatonin, valerian, *Ginkgo biloba, Serenoa repens*.

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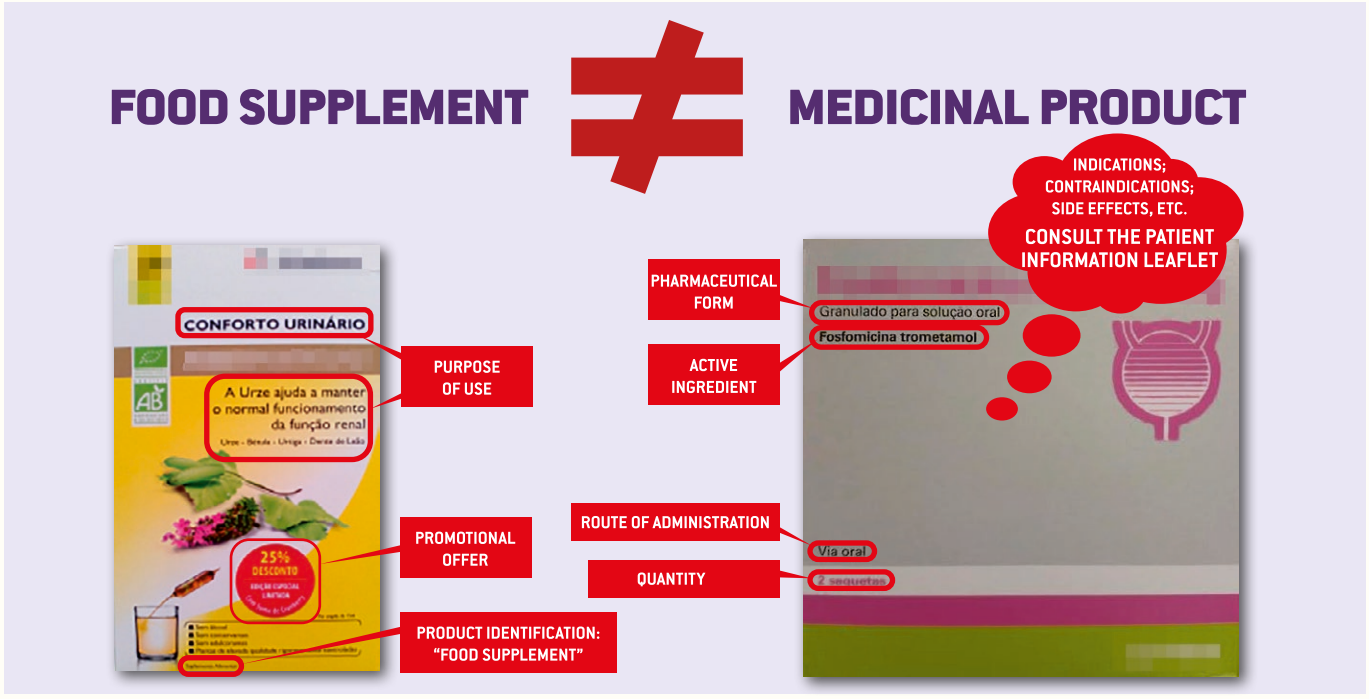
Groups and categories of food supplements

Vitamins and minerals		E.g.: *Vitamin A, vitamin D, calcium*
Plants and herbal extracts		*Aloe vera, Gingko biloba, Panax ginseng*
Other ingredients	**Fibre and Protobiotics**	*Inulin, Lactobacillus acidophilus, other types of yeast*
	Essential fatty acids	*Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA), Gammalinoleic acid*
	Aminoacids and Enzymes	*L-arginine, taurine, coenzyme Q10*

Food supplements can only be made available to the endpoint consumer as pre-packaged products. They are marketed in dosed forms (capsules, tablets, pills, powder in sachets, fluid in ampoules, drop vials and other similar forms) to be administered in measured units of small quantities.

Differently from foods in general, their placement in the market has to be preceded by notification to the corresponding regulatory authority – the Portuguese National Authority for Foods and Animal Health (**DGAV (Direção Geral de Alimentação e Veterinária)**. It does not involve running safety trials. Their safety is to be ensured by the economic operators through compliance with the food safety regulations applicable across the whole of the European Union.

In accordance with applicable legislation, labelling references and forms of advertising are limited and defined as in the examples in the figure below:



Foods make up an open system that is subjected to various forms of interaction and interference. At times adverse reactions may occur that can be related to the consumption of food supplements. Collecting and analyzing these data is very important as far as food safety and public health protection are concerned. This is the role of the regulatory authority DGAV, which provides a form in its web portal for reporting adverse reactions. This form should be filled out and sent in preferably by email to **Direção de Serviços de Nutrição e Alimentação** (Food and Nutrition Services Department) at DGAV: **dsna@dgav.pt**

Cristina Mousinho, Fátima Hergy

Reference:

[1] *https://www.repository.utl.pt/bitstream/10400.5/8229/1/Carateriza%C3%A7%C3%A3o%20do%20mercado%20portugu%C3%AAs%20de%20suplementos%20alimentares%20em%202014%20final.pdf (accessed on 31-03-2017)*

Vitamin K antagonist anticoagulants:
Risk of Calciphylaxis

Quick Read
Just like with warfarin, calciphylaxis can occur in association with other coumarin anticoagulants.

Classic anticoagulants, also known as coumarin agents, are often called vitamin K antagonists (VKAs) since that is the basis of their mechanism of action. Biosynthesis of plasma coagulation factors II, VII, IX and X is vitamin K dependent. Vitamin K is also involved in the biosynthesis of anticoagulant proteins C and S. For a full anticoagulant effect pre-formed factors II, VII, IX and X have to be eliminated. These factors have varying half-lives (60, 6, 24, and 40 hours, respectively),[1,2] which explains why the therapeutic effect of VKAs is not immediate.
Calciphylaxis is a rare, high-mortality vascular calcification and skin necrosis syndrome of mostly obscure pathophysiology. It is thought that it may arise from a therapy-induced imbalance in vitamin-K-dependent proteins and coagulation factors caused by their diverse half-lives. A marked decrease in the concentration of factors and proteins with a short half-life contrasts with a slow reduction in the concentrations of factors and proteins with longer half-lives. This discrepancy in concentrations induces a period of pro-thrombotic effect which causes obstruction of small vessels and hence poor blood circulation and the appearance of necrotic lesions.[3]

Based on cases from the literature, a safety signal (suspected safety problem) has previously been raised for warfarin and calciphylaxis (**see Boletim de Farmacovigilância, Volume 20, Nr. 3, September 2016**). Subsequently, an assessment was initiated regarding acenocoumarol, phenprocoumon, fluindione and fenindione as well. Once all the available data had been analyzed, and similarly to previous updates to the SmPC and PIL of warfarin, the PRAC at EMA recommended the following changes to the wording of the SmPCs of medicinal products containing acenocoumarol, phenprocoumon, fluindione and fenindione:

4.4. Special warnings and precautions for use

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking vitamin K antagonists including <product name>, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with <product name>.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'not known': Calciphylaxis

Beatriz Tavares da Costa

References:
[1] *Silva PM. Velhos e novos anticoagulantes orais. Perspetiva farmacológica. Revista Portuguesa de Cardiologia 31(1) 1-9, 2012. Disponível em: http://www.elsevier.pt/pt/revistas/revista-portuguesa-cardiologia-334/artigo/velhos-e-novos-anticoagulantes-orais-perspetiva-farmacologica-S087025511270034.*
[2] *Rang HP et al. Rang & Dale's Pharmacology 8th Ed., 2016.*
[3] *Silvestre, JMS et al. Skin necrosis induced by vitamin k antagonists. Jornal Vascular Brasileiro 8 (4), 344-346, 2009.*

Educational Materials published in the Infomed product information webpage

Medicinal product (DCI)	Click on the links (in Portuguese)
Ilaris (canakinumab)	***Educational materials for physicians*** Informação importante de segurança para o médico sobre o tratamento da Artrite Idiopática Juvenil Sistémica (AIJs) – 1.ª versão Informação importante de segurança para o médico sobre o tratamento de Artrite Gotosa (AG) – 2.ª versão Informação importante de segurança para o médico sobre o tratamento de Síndromes Periódicos associados à Criopirina (CAPS) – 4.ª versão For rheumatologists and paediatricians. ***Educational materials for patients*** Cartão de alerta para o doente (AG) – 2.ª versão To be handed out to patients with gouty arthritis. Cartão de alerta para o doente (AJIs) – 1.ª versão Guia de administração para o doente (pó para solução injetável) – 1.ª versão Guia de administração para o doente (pó e solvente para solução injetável com kit de administração) – 1.ª versão To be handed out to patients with Systemic Juvenile Idiopathic Arthritis. Cartão de alerta para o doente (CAPS) – 4.ª versão Guia de administração para o doente (pó para solução injetável) – 4.ª versão Guia de administração para o doente (pó e solvente para solução injetável com kit de administração) – 2.ª versão To be handed out to patients with Cryopyrin Associated Periodical Syndromes). Published on 09-03-2017
Yervoy (ipilimumab)	***Educational materials for healthcare professionals*** Guia para Prescrição – 3.ª Versão For oncology specialist physicians, dermatology departments, directors of oncology departments, directors of day care hospitals, and pharmaceutical services. ***Educational materials for patients*** Cartão de Alerta do doente – 3.ª Versão Guia com informação para o Doente – 3.ª Versão Published on 09-03-2017

Compiled by Magda Pedro

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics