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Editor's Notes

Weight loss typically becomes a sudden priority for many people as summer sets in, some patients embarking in unrealistic or irrational pursuits. The safety profiles of some of the medicines that are more often associated with weight control programmes are reviewed in this issue. The Boletim's section on adverse reactions to phytotherapeutic agents is entirely dedicated to herbs frequently used by consumers for that purpose.

Also in this issue: macular oedema as a potential adverse reaction to look out for in diabetics taking rosiglitazone; a possible association between paroxetine and congenital malformations under study; and warnings concerning the use of tacrolimus and pimecrolimus in atopic dermatitis.

Rosiglitazone and Risk of Macular Oedema

Rosiglitazone is a member of the thiazolidinedione class of oral antidiabetic agents whose mechanism of action involves decreasing resistance to insulin in fatty, musculoskeletal and liver tissues. It is marketed as rosiglitazone maleate and in a rosiglitazone maleate + metformin chlorhydrate combination, and is indicated for the treatment of type 2 diabetes mellitus.

Recently in the USA rare cases of visual disturbance associated with **macular oedema or worsening of pre-existing macular oedema** have been reported in patients on rosiglitazone. In some instances, there was clinical improvement and even full resolution upon discontinuation of the drug. In most reported cases, the patients also had **fluid retention, peripheral oedema, or weight gain**. Patients treated with rosiglitazone in general showed characteristics of greater severity or progression of their underlying condition comparatively to patients on other oral antidiabetic agents.

Macular oedema is often associated with diabetic retinopathy, and may occur without any other clinical signs of retinopathy. It becomes more frequent as the latter progresses. The **main risk factors** for macular oedema include **duration of diabetes, presence of diabetic retinopathy, hypertension, and poor glycaemic control**.

Assessment by the European medicines authorities of the relationship between macular oedema and rosiglitazone, and of a possible thiazolidinedione class effect is ongoing. Given the seriousness and rarity of this problem, **withdrawal of therapy and an ophthalmologic consultation should be considered in patients taking rosiglitazone who have deterioration of their visual acuity**, namely clouded or distorted vision, decreased adaptation to darkness or decreased sensitivity to colours.

Paula Roque

- Colucciello M. Vision loss due to macular edema induced by rosiglitazone treatment of diabetes mellitus. Arch Ophthalmol. 2005; 123(9):1273-5.
- Kendall C, Wooltorton E. Rosiglitazone (Avandia) and macular edema. Can Med Assoc J. 2006;174:623-623.

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
IL	Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

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Paroxetine in Early Pregnancy and Risk of Birth Defects

An analysis of data on consequences of therapy with paroxetine during pregnancy has generated a potential signal of increased incidence of congenital malformations in newborns whose mothers had taken paroxetine, especially during their first trimester of pregnancy. Most of those birth defects were cardiovascular, involving the atrial septum and mostly the **ventricular septum**.

According to available evidence, the risk of a child being born with the above type of congenital defects is around 1:100 in the general population. This new data points to a **risk** of approximately **2:100** following maternal exposure to paroxetine. It should be noted however of that, by far, **most** women who had been on paroxetine during their pregnancies did give birth to **healthy** babies.

No causal relationship between paroxetine and the above events has been so far established. This is due to epidemiological data being very limited by the rarity of the condition, and to the fact that the mechanism underlying those birth defects is still not known. Epidemiological studies do however sujgest such a risk, and more data is needed to decide whether there is indeed a causal relation between congenital malformations and paroxetine therapy during pregnancy. It should nevertheless be borne in mind that the increase in relative risk is small when offset by the potential risks to the foetus arising from untreated maternal depression.

Currently available data makes it relevant to ponder **therapeutic alternatives** for pregnant women or women contemplating pregnancy, at least for as long as this issue is not fully resolved. In those situations where treatment with paroxetine needs to be discontinued, this should be done gradually in order to minimise the risk of withdrawal symptoms.

- Ericson A, Kallen B, Wilholm BE. Delivery outcome after the use of antidepressants in early pregnancy. Eur J Clin Pharmacol 1999;55:503-508.
- Hallberg P; Sjöblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. J Clin Psychopharmacol. 2005; 25(1):59-73.
- Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med. 2006 Feb;160(2):173-6.
- Williams M, Wooltorton E. Paroxetine (Paxil) and congenital malformations. Can Med Assoc J. 2005 Nov 22;173(11):1320-1

Paula Roque

Protopic®/Protopy® (tacrolimus) and Elidel® (pimecrolimus): special precautions of use

Protopic®/Protopy® (tacrolimus) and Elidel® (pimecrolimus) are topical immunosupressor agents indicated for the treatment of **atopic dermatitis** (eczema).

Following **reports of cases of skin cancer and lymphoma** (including its cutaneous form) in patients who had used these medicines, EMEA conducted a safety reassessment and concluded that the benefit associated with these agents outweighs their risk. Based on available data, a causal relationship between Protopic®/Protopy® or Elidel® and skin cancer and lymphoma could not be established. For monitoring purposes, EMEA has therefore asked MA Holders to provide additional data on the long term safety profile of these agents. INFARMED wishes to highlight the main recommendations that have just been approved on the use of Protopic®/Protopy® and Elidel®, and which will from now be included in their SPCs and Information Leaflets:

Recommendations to physicians who prescribe Protopic®/ Protopy®(tacrolimus) or Elidel®(pimecrolimus):

- Use only in patients **older than 2 years** with mild to moderated disease (Elidel®), or with moderate to severe disease (Protopic®/ Protopy®).
- Use only **whenever topical corticosteroid therapy cannot or should not be used**, namely: when the skin area to be treated is not appropriate (e.g.. face and neck), whenever corticoid treatment is not effective, or the patient does not tolerate it.
- Only physicians experienced in both diagnosing and treating atopic dermatitis should start therapy with these medicines.
- They must only be applied on affected skin areas and in a thin layer.
- The medicine's smallest effective dose should be used, on a once-a-day regime if at all possible.
- Continuing, long-term use should be avoided. Treatment should be stopped as soon as the eczema resolves.
- Should the patient deteriorate or show no improvement, diagnosis should be reviewed and other therapeutic options should be considered.
- These medicines should not be used in adults or children who are immunocompromised by either disease or therapy.
- They should not be applied in malignant or pre-malignant neoplastic lesions.
- Should the patient have any lymphadenopathies at the time treatment is to be started, additional investigations should be carried out and the patient kept under surveillance.

You can access further information in the EMEA web site at: **www.emea.eu.int/pdfs/general/direct/pr/988206en.pdf**

Alexandra Pêgo

What should one report?

Every suspected **serious** adverse reaction, even if already previously described. Seriousness criteria include:

- causing death
- life threatening
- prompting hospital admission
- prolonging hospital stay
- resulting in persistent or significant incapacity
- suspected congenital anomaly or malformation
- does not meet any of the above criteria but health professional considers it to be a serious ADR

Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)

Medicines and Food Supplements used as Adjuvants in Weight Control Regimes – Safety Profiles

Health professionals are often addressed by patients in Spring and Summer asking for prescriptions and advice on medicinal and food supplements (so-called *natural products*) for weight control purposes. Indiscriminate use of these products can cause serious problems arising from ill use and interactions.

The only active ingredients approved in Portugal for weight control are **sibutramine** and **orlistat**. There is however a long list of **herbs and plant-derived products** that are used for controlling weight. **Chitosan**, a non-medicinal product, seems to have shown some activity in a few studies as an aid to weight reduction. There is moreover an even longer list of **laxatives** which are chronically used **off-label** to control weight, and which may be associated with hazards such as dehydration, tolerance, irritation of the intestinal mucosa, etc.

Choosing the best method to reduce weight depends on a number of factors, especially[1]:

1. Body mass index
2. Concomitant conditions (hypothyroidism and other hormonal conditions) that should be simultaneously kept under control
3. Obesity-related risk factors (type 2 diabetes, dyslipidaemia, etc.)
4. Tolerance to expected adverse reactions (namely for orlistat)
5. Patient's lifestyle (sedentary habits, alimentary behaviour, etc.)
6. Results of previous attempts to lose weight (pharmacologically or otherwise);

Sibutramine[2,3]

Sibutramine is indicated as adjuvant therapy in a weight control programme for obese patients with a body mass index (BMI) equal to or higher than 30 kg/m^2, or equal to or higher than 27 kg/m^2, and who present with other obesity-related risk factors. It should only be used in patients who have not appropriately responded to previous weight loss regimes (response to a weight loss regime is considered appropriate if there is weight loss of over 5% in a 3-month period in an obese patient). It is recommended that treatment with sibutramine be accompanied by a persistent change in alimentary habits and behaviour, which is especially important if one is to avoid regaining weight once the medicine is discontinued.

Sibutramine, similarly to some antidepressants, is a **serotonin and norepinephrine re-uptake inhibitor**. Weight loss is mainly due to a reduction in the quantity of food ingested, since sibutramine promotes **satiety**. However, the drug's **thermogenic effect** may also contribute towards weight reduction. Reducing the quantities of ingested food has been shown to be beneficial also for controlling blood lipid and glucose levels in obese patients.

Treatment with sibutramine may go on for up to **one uninterrupted year**. However, it should be discontinued in patients who:

a. Do not respond adequately (do not sustain a minimum 5% weight reduction after 3 months, or whose weight reduction has stabilised at a less than 5% reduction of the initial weight)

b. Have regained 3 kg or more following an initial weight loss.

Sibutramine is contraindicated or requires special precautions of use in **psychiatric** and **neurological** conditions, in **hypertensive patients** or in patients with a **past cardiac history**, among others. Although sibutramine has not been associated with primary pulmonary hypertension, and on account of general concerns about antiobesity medicines, patients should be monitored routinely for suspicious signs and symptoms.

There may be **interactions** with any drug metabolised by CYP4503A4, with drugs which increase brain serotonin levels or affect blood pressure and heart rate, and with alcohol. Sibutramine should therefore be prescribed only when traditional strategies (low-calorie diet and exercise) have been shown to be ineffective or insufficient to attain a given weight loss goal.

Orlistat[4]

Orlistat is indicated, in association with a moderately calorie-deprived diet, for the treatment of obese patients whose BMI is equal to or higher than 30 kg/m^2, or equal to or higher than 28 kg/m^2, and who have other obesity-related risk factors. Orlistat therapy should only be started after a previous low-calorie diet for 4 consecutive weeks has on its own originated a minimum 2.5 kg weight loss. It should be discontinued if after 12 weeks the patient has not lost at least 5% of his/her body weight at treatment outset.

Orlistat is a prolonged inhibitor of intestinal lipases. Its therapeutic action takes place in the gastric and intestinal lumen, through inactivation of the enzymes that hydrolyse fat from foods, and by promoting fat elimination in faecal matter (i.e. by impeding its absorption). This mechanism of action is intimately connected to **adverse reactions** that can be observed relatively frequently such as steatorrhoea, urgency in defection, increased defecation and faecal incontinence, and whose intensity is **related to the amount of fat ingested**. On the other hand, orlistat decreases absorption of lipid-soluble vitamins (A, D, E, K). For that reason, **vitamin supplementation** taken **two hours before** orlistat is often recommended.

Although there do not seem to be any changes in **warfarin**'s pharmacokinetics during treatment with orlistat, decreased vitamin K absorption may increase warfarin's anticoagulant effect, which makes **INR monitoring** advisable.

Chitosan[5]

Chitosan is a water-soluble polymer similar to cellulose which is derived from chitin from the exoskeleton of marine crustaceans (whence it is usually extracted). It can also be found in fungi, yeast, marine invertebrates, and arthropods. Its intestinal absorption is minimal, and it is mostly excreted in the faeces. It may **cause weight reduction** and **decrease LDL-cholesterol levels** and **raise HDL-cholesterol levels** by its positively charged amine groups attaching to negatively charged fatty acid and biliary acid-derived molecules, thus preventing their absorption.

Adverse reactions described in studies are mostly GI discomfort, flatulence, diarrhoea, nausea and constipation. There is no apparently significant increase in the excretion of non-digested fat in faeces.

Chitosan **should not be used in patients who are allergic to shellfish**, since it is extracted from marine crustaceans. Moreover, given its origin, chitosan-based products may be contaminated with heavy metals (lead, mercury, iron, copper); their use should therefore be **avoided in children, pregnant women and during breastfeeding**.

Though there are no drug interactions described for chitosan, in theory it may decrease the absorption of lipophillic medicines and lipid-soluble vitamins.

Herbs and plant extracts

They usually have no robust evidence of effectiveness and their therapeutic use is not approved. Mechanisms could include increased lipolysis, induction of satiety, etc. Patients with hyperthyroidism, diabetes, kidney failure and high blood pressure, as well as children and pregnant women, should seek medical advice before using these products.

Laxatives

They have a potential for interaction with any drug that acts on or is absorbed in the intestine. They should only be used in cases of true constipation and never as an *emergency* solution for sudden weight loss.

Increasing awareness of society and of health professionals of the cardiovascular and endocrinologic risks of obesity has led to higher levels of consumption of medicines and other products for losing weight. Any serious adverse effect or drug interaction should be reported to INFARMED.

To report ADRs or Drug Interactions Pharmacovigilance Dept.
ADR Monitoring Sector
farmacovigilancia@infarmed.pt
Ph: 217987141
Fax: 217987155

1. Better Than Slim Chances for Orlistat and Sibutramine to Promote Weight Loss. Drug Ther Perpect 2000; 15 (12): 1-6.
2. Resumo das características do Medicamento. Reductil 10 mg cápsulas duras. Disponível em www.infarmed.pt
3. Resumo das características do Medicamento. Reductil 15 mg cápsulas duras. Disponível em www.infarmed.pt
4. Resumo das características do Medicamento. Xenical 120 mg cápsulas duras. Disponível em www.infarmed.pt
5. Shields K M, Smock N, McQueen C E, Bryant P J. Chitosan for weight loss and cholesterol management. AM J Health-Syst Pharm 2003; 60 (13): 1310-1313.

Maria Susana Gonçalves

Safety Profiles – Summary*

	Sibutramine	Orlistat	Chitosan
Therapeutic indications	BMI>30 kg/m^2, or IMC>27 kg/m^2 with risk factors.	IMC>30 kg/m^2, or IMC>28 kg/m^2 with risk factors.	No approved therapeutic indication.
Dosage	10 to 15 mg once a day.	120 mg immediately before, during, or up to one hour after each main meal.	1 to 5 g/day divided by meals.
Mechanism of action	Promotes satiety.	Inhibition of fat digestion and absorption.	Decreased absorption of fatty acids.
Contraindications	**Hypersensitivity.** **Psychiatric and neurological conditions.** **Non-controlled hypertension or history of cardiovascular or cerebrovascular conditions.** **Severe liver or kidney failure.** **Hyperthyroidism, pheochromocytoma.** **Closed-angle glaucoma.** **Benign prostatic hypertrophy.**	**Hypersensitivity.** **Chronic malabsorption syndrome.** **Cholestasis** **Pregnancy and breastfeeding.**	Not described.
Special precautions of use	Simultaneous use of sympathomimetics (e.g.: pseudoephedrine, topical nasal decongestants...) History of depression. Open-angle glaucoma, or family history of high intraocular pressure. Driving or use of dangerous machinery. **In follow-up check-ups look for progressive breathlessness, chest pain, ankle oedema.** **Additional precautions for the 15-mg daily dosage:** Epilepsy. Family history of motor or verbal disorders. Liver or kidney dysfunction. **Blood pressure and heart rate should be monitored throughout treatment.** Contraception for women at child-bearing age.	Treatment with oral antidiabetics. Consider administering vitamin supplements in prolonged treatment.	Do not use in patients **allergic to shellfish,** children, pregnant and breastfeeding women.
Drug Interactions	Ketoconazole, itraconozole, erythromycin, clarithromycin, troleandromycin, cyclosporine, rifampin, phenytoin, carbamazepine, phenobarbitone, dexamethasone, and any medicines that raise brain serotonin levels.	Acarbose, biguanides, appetite suppressants, warfarin, cyclosporine.	Not described. May potentially interfere with absorption of lipophillic drugs and lipid-soluble vitamins.
Adverse reactions	**Very frequent**: constipation, dry mouth, insomnia. **Frequent**: tachycardia, palpitations, raised blood pressure/hypertension, vasodilatation, nausea, worsening of haemorrhoids, Giddiness, paraesthesia, headache, anxiety, sweating, dysgeusia.	**Very frequent**: Fatty stains, gaseous discharges, urgency in defecation, fatty/oily stool, increased defecation, faecal incontinence. **Frequent**: Abdominal pain/malaise, flatulence, watery stool, rectal pain/discomfort, dental or gum lesions, infections, headache, fatigue, anxiety.	GI discomfort, flatulence, diarrhoea, nausea, and constipation.

***Full SPCs should be looked up for complete details.**

Maria Susana Gonçalves
Sofia Guimarães

Medicinal plants used for weight control* described adverse reactions

- **Fucus** *(Fucus vesiculosus)*
  - arrhythmia?, renal toxicity?
  N.º of Medline citations: 2
  Main uses described: (thyroid?) stimulant.

- **Garcinia cambogia, HCA (hydroxycitric acid)** *(Garcinia cambogia)*
  - ?
  N.º of Medline citations: 2
  Main uses described: stimulant, appetite suppressant.

- **Konjac glucomannan, devil's tongue** (Amorphophallus konjac)
  - liver toxicity
  N.º of Medline citations: 4
  Main uses described: satiety inducer, laxative, blood glucose lowering, blood cholesterol lowering.

- **Guarana** *(Paullinia cupana* Kunth)
  - nervousness, insomnia, other effects of hypersensitivity to caffeine (its main constituent)
  N.º of Medline citations: 19
  Main uses described: stimulant, appetite suppressant.

- **Ma Huang, Ephedra** *(Effedra sinica* Stapf.)
  - associated with liver toxicity, high blood pressure, acute coronary events, stroke!
  N.º of Medline citations: 168
  Main uses described: stimulant, appetite suppressant, bronchodilator (sympathomimetic).

- **Maitake mushroom** *(Grifola frondosa)*
  - ?, potential mix-up with toxic mushrooms
  N.º of Medline citations: 2
  Main uses described: immunostimulant, anti-cancer symptoms, blood glucose lowering, weight loss.

- **Java tea** *(Orthosiphon stamineus)*
  - liver toxicity
  N.º of Medline citations: 2
  Main uses described: diuretic, antilithiasic.

** NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. No therapeutic indication or endorsement of use should by this publication should be inferred.*
** NB 2: The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".*