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From the Editor

Ongoing surveillance of medicines and measures to minimize newly detected risks can together be construed as a risk-benefit weighing strategy, which allows for patients who most benefit from a given treatment to keep having access to it, while at the same time protecting subgroups of patients with specific risk profiles who would be exposed to a higher likelihood of a less favourable outcome. Novel restrictions to the use of the antiosteoporotic agent strontium ranelate are an example of such a strategy.

In this issue clopidogrel is under the spotlight for two diverse safety reasons: possible allergic cross-reactivity with ticlopidine, and a (very low) risk of eosinophillic pneumonia.

More in this issue: almitrine withdrawn, liver function needs to be monitored when flupirtine is used, safety reviews of oral contraceptives containing ciproterone + ethinylestradiol and of renin-angiotensin modifying agents, and intravenous paracetamol prescribing and administration error minimization revisited.

Online reporting of adverse drug reactions by health professionals and patients

Portal RAM for ADR reporting. Online forms for both health professionals and patients.

How can I report an adverse reaction?

- **ADR Portal (Portal RAM):**
  http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
- **Report Card online printout link:**
  www.infarmed.pt/portal/page/portal/INFARMED /MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM
- **Postage Paid Card**

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Strontium Ranelate: Restrictions of use

EMA has recommended that the use of the strontium ranelate containing medicinal products Protelos® e Osseor® be restricted, following an assessment of new safety data which demonstrated an increased risk of **serious cardiac problems**, including myocardial infarction.

In fact, as a result from a routine risk-benefit assessment of those products, the Pharmacovigilance Risk Assessment Committee (PRAC) at EMA found relevant data emerging from the Periodic Safety Reports (PSRs) concerning a clinical trial including about 7,500 patients. This trial pointed to an increased risk of myocardial infarction in postmenopausal women taking Protelos® ou Osseor®, in comparison with women taking placebo (1.7% versus 1.1%), with a relative risk of 1.6 (95% IC; 1.07 to 2.38). There was also a difference in the number of serious cardiac events with these medicines in two studies, one in osteoporotic men and another in osteoarthritic patients. No increased risk of mortality was seen. Given other risks also previously confirmed by EMA in 2012 (serious risk of **venous thromboembolism** and of **rare skin reactions**), the PRAC concluded that restrictions to the use of these medicines would be in order if their risk-benefit ratio were to remain favourable.

EMA therefore recommends that those products be used **only for the treatment of serious osteoporosis in postmenopausal women at high risk of fractures**, and in **men with an increased risk of fractures**.

Restrictions regarding patients with heart or circulation problems have also been included to minimize the cardiovascular risk. They include **contraindications** in patients with current or past **ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease**, as well as with **uncontrolled arterial hypertension**.

Recommendations for prescribers to ensure the safe and effective use of these medicines include a decision to prescribe only after the patient's individual risks have been evaluated. The risk of developing a cardiovascular condition in particular, should be assessed **before prescribing** and **at regular intervals** during treatment.

Should the patient develop ischaemic heart disease, peripheral arterial disease or cerebrovascular disease, or should their arterial hypertension not be under control, treatment is to be **suspended**.

In addition to the above measures, EMA has decided to initiate a full review of all available risk-benefit data (including cardiovascular) of Protelos® and Osseor®. The results will be made public as they become available.

What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorisation
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
SPC	Summary of the Product's Characteristics

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Clopidogrel
Risk of Cross Reactions

Clopidogrel is an antithrombotic agent used in the prevention of atherothrombosis in peripheral arterial disease, stroke, acute coronary syndromes including myocardial infarction, and in atrial fibrillation. The centrally-authorized medicinal products containing clopidogrel have been used by an estimated number of over 115 million patients worldwide (between 1998 and 2010).

A retrospective study conducted in 76 patients who had developed **allergy** to clopidogrel or to ticlopidine has shown that approximately one third of the patients sustained the same reaction when subsequently treated with the other drug.[1] More recently, during routine signal detection activities, twenty spontaneous case reports of relevance were captured within EudraVigilance (European adverse reactions database), which supported a signal regarding potential cross-reactivity between ticlopidine and clopidogrel.

The PRAC at EMA analyzed this issue and concluded that there were indeed data pointing to **cross-reactivity between clopidogrel and ticlopidine and among tienopyridines in general**. A recommendation has thus been made for corresponding changes in the information materials of products containing clopidogrel.

Margarida Guimarães

[1] Lokhandwala JO et al. Circ Cardiovasc Interv. 2009 Aug;2(4):348-51.

Clopidogrel
Risk of Eosinophillic Pneumonia

Based on a review of seven cases contained in EudraVigilance (the European database of adverse reactions), EMA has identified a potential safety signal for eosinophillic pneumonia. The PRAC has confirmed that this reaction had been only **very rarely** reported, given the high exposure to clopidogrel worldwide. However, the reviewed data did support a causal association between clopidogrel and risk of eosinophillic pneumonia. Since this is a serious adverse effect which calls for immediate treatment and which may require treatment interruption, the information materials of products containing clopidogrel are to be updated accordingly. A reference to the risk of eosinophillic pneumonia as a very rare undesirable effect will therefore be included.

Margarida Guimarães

Flupirtine
Liver Function

EMA has started a safety review of the medicinal products containing flupirtine following an increase, detected by the German medicines agency, in the number of reports of liver ADRs ranging from an **asymptomatic rise of liver enzymes to liver failure**. In total, 330 cases of hepatic problems have been reported, fifteen of which were fatal or resulted in a liver transplant.

In addition, the German agency concluded that data supporting the effectiveness of flupirtine for long term relief of pain are scarce. The PRAC at EMA also confirmed that, contrarily to the studies on the use of flupirtine for the treatment of acute pain, data on long term use are not very robust; there do not seem to be enough data pointing to benefits from using this medicine for periods longer than four weeks.

As for hepatic safety, the PRAC has concluded that the duration of treatment seems to be of relevance for the occurrence of liver problems. Indeed, no cases of liver failure or hepatic transplant have been reported in patients being treated for **two weeks or less**.

In order to ensure that the benefits of flupirtine remain higher than the corresponding risks, the PRAC at EMA recommends the following for the time being:

- Medicines administered orally or in suppository form should be used for the treatment of acute (short term) pain in adults who cannot use other analgesics, such as NSAIDs and weak opioids;
- Treatment should **not** exceed **two weeks**.
- The patients' **liver function** should be monitored **after each week** of full treatment; the latter should be suspended in case of signs of liver problems.
- Flupirtine should not be used in patients who:
  - have preexisting liver conditions;
  - abuse alcohol or are addicted to alcohol;
  - are taking other hepatotoxic drugs.

In Portugal the only products containing flupirtine with a MA are for oral administration and only Metanor® 100 mg capsules is currently being marketed.

Margarida Guimarães

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Ciproterone acetate 2 mg Ethynilestradiol 35 µg: Conclusions from safety review

The PRAC at EMA has assessed the safety data available on the risk of thromboembolism associated with products containing ciproterone acetate 2 mg + ethynilestradiol 35 µg, based on European post-marketing data and published literature. Health professionals, patient organizations and the public at large were also invited to submit data they deemed relevant for assessment. The conclusion was that the risk of venous **thromboembolism** associated with these medicines is **1.5 to 2 times** higher than that of levonorgestrel-containing oral combined contraceptives and that it is **similar** to that of contraceptive agents containing gestodene, desogestrel or drospirenone.

In the meantime and in general terms, the risk of venous thromboembolism associated with ciproterone + ethynilestradiol is **recognizedly low**. Warnings included in the SPCs and Information Leaflets of these products address both physicians and patients in this respect.

In terms of effectiveness, the available data **support the use** of products containing ciproterone acetate 2 mg + ethynilestradiol 35 µg for the treatment of moderate to severe **acne** in androgen-dependent women and/or in hirsutism, at child-bearing ages. For **alopecia** however, **risks outweigh benefits**.

In order to minimize the risk of thromboembolism, PRAC has recommended the additional measures that follow.

Recommendations to health professionals

- Medicinal products containing ciproterone acetate 2 mg + ethynilestradiol 35 µg should only be prescribed for the treatment of **moderate to severe** androgen-dependent **acne** (with or without seborrhoea) and/or for hirsutism in women of child-bearing age.
- In the treatment of acne, these medicines should only be prescribed when t**opical therapy or systemic antibiotics** have **not** been **effective**.
- Since products containing ciproterone acetate 2 mg + ethynilestradiol 35 µg also act as hormonal contraceptives, they should **not** be **used simultaneously with other hormonal contraceptives**.
- Doctors should **reassess** the patients who are taking these medicines in a follow-up appointment.

Recommendations to patients

- If you are taking medicinal products containing ciproterone acetate 2 mg + ethynilestradiol 35 µg for indications other than acne and/or hirsutism, book a non-urgent appointment with your attending physician so that your treatment can be reviewed.
- You should not stop taking the medicine until you speak to your doctor. These products can also be used as contraceptives. Therefore, if you stop taking them, other contraceptive methods will have to be used to prevent any unwanted pregnancy.
- Tell your doctor immediately should you have any symptoms such as leg pain or swelling, breathlessness, or acute chest pain.

Catarina Costa

Renin-Angiotensin System Modifiers: Safety review

EMA has started a safety review to assess the impact of simultaneously using more than one renin-angiotensin modifying agent in the treatment of hypertension and congestive heart failure.

Renin-angiotensin system modifiers can act in three different ways: as angiotensin receptor antagonists (ARA), as angiotensin-converting enzyme (ACE) inhibitors and as direct renin inhibitors (e.g., aliskiren).

Given the results from published studies, including a recent metaanalysis of 33 clinical trials involving over 68,000 patients,[1] EMA's review aims to evaluate whether the concomitant use of several renin-angiotensin system modifiers increases the risks of hypercalcaemia, reduced blood pressure and renal failure, in comparison to using one type of modifier only. Another objective is to see whether the benefits of combined therapy in terms of overall mortality are higher than those obtained from using one modifier in isolation.

In February 2012, EMA had already concluded that the combination of aliskiren with an ACE inhibitor or with an ARA could increase the risk of collateral cardiac, circulatory and renal effects [http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=6055877, in Portuguese]. Of the recommendations then made, the following are highlighted:

- Medicines containing aliskiren, should not be prescribed in combination with ACE inhibitors or ARAs to patients with types 1 or 2 diabetes or with moderate to severe renal failure. In those cases, an alternative therapy should be considered.
- Continuing therapy with medicines containing aliskiren in combination with ACE inhibitors or ARA should be carefully weighed in the remaining patients.

EMA and Infarmed are following up on these issues and will disseminate any relevant new data.

Magda Pedro

[1] Makani H et al. BMJ, 2013 Jan 28; 346:f360.

Almitrine Revocation of marketing authorization

A almitrina é um derivado piperazínico que estimula a respiração atuando como agonista dos quimiorrecetores periféricos carotídeos. Estava indicada no tratamento de insuficiência respiratória com hipoxemia na bronquite obstrutiva. Em Portugal existe apenas um medicamento com AIM contendo almitrina (Vectarion®), o qual não se encontra comercializado.

A Agência Francesa do Medicamento solicitou uma revisão de segurança destes medicamentos na sequência da identificação em alguns doentes de efeitos secundários incluindo **perda de peso** e **neuropatia periférica** potencialmente grave e de longa duração.

O PRAC da EMA considerou que as evidências disponíveis não suportavam as indicações terapêuticas da almitrina como parte do tratamento da Doença Pulmonar Obstrutiva Crónica (DPOC) e que existem alternativas terapêuticas disponíveis. Assim, foi concluído que os riscos dos medicamentos administrados por via oral contendo almitrina **superam** os seus **benefícios**, pelo que foram revogadas todas as AIM desses medicamentos na União Europeia.

Margarida Guimarães

Paracetamol IV
Risk of Accidental Overdose

Following the assessment of available data on the risk of medication errors with paracetamol for IV infusion which caused instances of accidental overdose in new-borns and low-weight adults, due to mistakes between milligram (mg) and millilitre (ml), EMA has decided on the need for MA Holders within the EU to implement risk minimization measures. These were grouped in a Risk Management Plan (RMP) and include, amongst others, updating the SPCs and Information Leaflets. They aim to make even clearer the prescription tables included, as well as to disseminate educational materials for health professionals which reinforce the importance of conforming to the existing recommendations for correct prescription, preparation and administration.

SPC dosage table and mode of administration section updates (highlights in bold and text adaptations for this publication only):

section 4.2 – posology and method of administration

Patient's weight	Dose per administration	Volume per administration	Maximum volume (10 mg/ml) per administration, according to upper limit of weight interval (ml)***	Maximum daily dose**
≤ 10 kg*	7,5 mg/kg	0,75 ml/kg	7,5 ml	30 mg/kg
> 10 kg to ≤ 33 kg	15 mg/kg	1,5 ml/kg	49,5 ml	60 mg/kg not more than 2 g
> 33 kg to ≤ 50 kg	15 mg/kg	1,5 ml/kg	75 ml	60 mg/kg not more than 3 g
> 50 kg with additional hepatic risk factors	1 g	100 ml	100 ml	3 g
> 50 kg without additional hepatic risk factors	1 g	100 ml	100 ml	4 g

* Premature new-borns: no safety and efficacy data are available for premature new-borns (see section 5.2).
** Maximum daily dose: The maximum daily dose given is for patients not receiving other medications containing paracetamol, and should be adjusted otherwise.
*** Patients weighing less will need smaller volumes.

The minimum interval between each administration should be **at least 4 hours**.

The minimum interval between each administration in patients with severe renal failure should be at least 6 hours.

Not more than 4 doses should be administered within a 24-hour period.

Method of administration:

Special care is needed when prescribing and administering this medicine in order to prevent dosage errors arising from confusing milligram (mg) and millilitre (ml), which may cause accidental overdose and death. Ensure that the correct dose is communicated and dispensed. **When prescribing, indicate the total dose both in milligram (mg) and in volume (ml)**. Make sure that the dose is measured and administered correctly.

This paracetamol solution should be administered as an **intravenous infusion lasting 15 minutes**.

Patients weighing ≤ 10 kg:

- The vial/bag should not be hung up and administered as a drip, given the small volume to be used in this population.
- The volume to be administered should be withdrawn from the vial/bag and diluted in a 0.9% saline solution or in a 5% glucose solution, up to one tenth (one volume in each nine volumes of diluent), and administered over a period of 15 minutes.
- Use a 5-ml or a 10-ml syringe to measure the appropriate dose for the child's weight and the appropriate volume, which should however never exceed 7.5 ml per dose.
- The professional in charge of preparing and administering the medicine should consult the dosage recommendations.

In the case of 50-ml and 100-ml infusion bottles, a 0.8 mm (21G needle) should be used to remove the desired volume and to vertically perforate the cap in the indicated spot.

The 50-ml infusion bottle can also be diluted in a 0.9% saline or in a 5% glucose solution up to one tenth (one volume in nine volumes of diluent). In this case, the diluted solution should be used up to one hour after preparation (including the infusion time).

Joana Oliveira

ADRs in the literature...

Orlistat seems not to be associated with risk of acute liver injury

In this self-controlled case study on the UK Clinical Practice Research Datalink population database, the authors aimed to determine a possible association between orlistat and acute liver injury. They studied the relative incidence of acute hepatic injury by linking primary care with hospital-based data spanning over a decade, and by comparing the periods in which over ninety thousand patients received orlistat versus the periods in which they had not. The **incidence** of acute hepatotoxicity was **higher** in the periods both **immediately before and immediately after the beginning** of the treatment with orlistat. This suggests that they were more probably related with changes in the patients' health condition arising from their decision to start the treatment rather than from a causality nexus with the drug.

Douglas IJ et al. BMJ 2013;346:f1936

ADRs in the literature...

Risk of Herpes Zoster not raised when Anti-TNF is started

It is known that patients with rheumatoid arthritis have a baseline increased risk of reactivation of herpes zoster (shingles). In this study the risk of shingles was compared when **anti-TNF versus non-biologic DMARD** therapy was started in a US cohort of patients with **rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis and ankylosing spondylitis**. The authors concluded that patients with rheumatoid arthritis and other chronic inflammatory diseases who are started on anti-TNF therapy, do not seem to be exposed to a higher risk of herpes zoster than those who begin to receive non-biologic therapeutic regimes.

JAMA. 2013;309(9):887-895. doi:10.1001/jama.2013.1099.

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