boletim de FARMACOVIGILÂNCIA

Ministério da Saúde

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

VOLUME 11
NUMBER 4
4TH QUARTER 2007

## Editor's Notes

*The safety of medicines could be described in a simplified way as the vector resulting from the balance between its therapeutic benefits and its potentially expected and unexpected risks. The assessment of the risk-benefit balance of medicines is a dynamic and continuing process aiming to protect patients as much as currently available knowledge allows. In many instances the safety assessment will confirm that the scales are tipped to the side of benefit, but sometimes the balance may be tipped unfavourably in such a way that the medicinal product may have to be withdrawn from the market. Thiazolidinediones are a good example of the former whereas lumiracoxib, clobutinol and aprotinin illustrate well the latter.*

## Strontium Ranelate and DRESS

Strontium ranelate is used for the treatment of osteoporosis in postmenopausal women, to reduce the risk of vertebral and femoral neck fractures. The daily recommended dose is one 2-g sachet once a day orally. Given the nature of the condition it targets this medicine is for long-term use

In the course of post-marketing monitoring, 16 cases, including two fatalities, of a hypersensitivity syndrome associated with the use of strontium ranelate were reported. This reaction is known as **DRESS** (**Drug Rash with Eosinophilia and Systemic Symptoms**).

### 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

**OR**

**National Pharmacovigilance Centre**
Tel: 217 987 140 - Fax: 217 987 155
E-mail: farmacovigilancia@infarmed.pt

**Northern Regional Pharmacovigilance Unit**
Tel: 225 573 990 - Fax: 225 573 971
E-mail: ufn@med.up.pt

**Lisbon and Tagus Valley Regional Pharmacovigilance Unit**
Tel: 217 802 120 - Fax: 217 802 129
E-mail: uflvt@sapo.pt

**Southern Regional Pharmacovigilance Unit**
Tel: 217 971 340 - Fax: 217 971 339
E-mail: urfsul@ff.ul.pt

The DRESS syndrome is a rare but serious and potentially fatal condition of unknown pathophysiological mechanism, which is characterised by skin reactions, fever, eosinophilia, adenopathies, and systemic envolvement (e.g.: hepatitis, interstitial nephropathy, and interstitial pulmonary disease). Clinical manifestations usually occur **between 3-6 weeks after therapy is started** and, in most cases, resolve with treatment discontinuation and administration of corticosteroids. Recovery can be slow however, and cases of relapse following interruption of steroid therapy have been reported.

Patients should be informed that in case a skin rash appears they should **immediately stop the treatment** and see their doctor. Patients who have stopped the treatment due to a hypersensitivity reaction must not be put back on strontium ranelate therapy again.

***Madalena Arriegas***

**INDEX CARD** | **Director:** Regina Carmona **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Alexandra Pêgo, Ana Araújo, Catarina Martins, Eugénio Teófilo, Fátima Bragança, João Ribeiro Silva, Madalena Arriegas, Paula Roque, Pedro Marques da Silva, Regina Carmona, Susana Gonçalves, **Advisory Board:** Vasco Maria, Luísa Carvalho, Helder Mota Filipe (INFARMED Executive Board); INFARMED Medicines Evaluation Committee. **Publisher:** INFARMED-Instituto Nacional da Farmácia e do Medicamento, Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, correio elertrónico: infarmed@infarmed.pt **Design and Prodution:** nsolutions - design e imagem, lda. **Printing:** Tipografia Peres **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 40.000

# Apnoea following vaccination in very premature infants

Infants born very prematurely generally are at greater risk of apnoea, defined as a respiratory pause of 20 seconds or longer, usually associated with bradycardia and for which no cause has been identified. This reaction could be ascribed to the infants' respiratory and neurological immaturity, and is apparently related with their degree of prematurity.

EMEA has recently conducted a review of all cases of apnoea in premature infants after immunisation with various vaccines, and the following was concluded:

* The occurrence of apnoea after vaccination is especially increased in this paediatric population. However, it was considered that this problem is not related to any vaccine in particular, rather to **vaccination in general** due to immaturity of the immune system.

* Regarding the definition of immaturity, the term "very premature" was agreed on, defined as **gestational age equal to or shorter than 28 weeks**, and this is the population at **greater risk** for post-vaccination apnoea.

* Since this problem seems to be associated with any vaccine given to this population irrespective of its route of administration, the SPCs should contain information reflecting currently available data, that is, infants born very prematurely are at higher risk for the occurrence of apnoea within the first two days after vaccination.

* However, since the benefit of vaccination is high in this paediatric group, immunisation should not be renounced. It is therefore recommended that these infants **be immunised and carefully monitored for 48-72 hours after vaccination**.

The SPC of all vaccines that might be administered at **up to 3 months of age** in infants born very prematurely will be updated in order to include the following information*:

**Section 4.4 Special warnings and precautions for use**

The potential risk of occurrence of apnoea should be considered, as well as the need for respiratory monitoring for 48-72 hours whenever administering the primary course of vaccination to very premature infants (born with ≤ 28 weeks of gestation), especially those with a history of respiratory immaturity. Since the benefits of immunisation are high in this paediatric group, vaccination should not be skipped or postponed.

**Section 4.8 Undesirable effects**

Apnoea in infants born very prematurely (≤ 28 weeks of gestation) (see section 4.4).

**Free translation from the Portuguese wording.*

**Madalena Arriegas**

# Epoetins:

**- risk of increased tumor progression and thromboembolic events in oncological patients**
**- cardiovascular risk in patients with chronic renal failure**

A Europe-wide safety evaluation concerning all epoetins has recently been concluded. Epoetins are used for the treatment of anaemia in patients with chronic renal failure and in oncological patients with non-myelogenous malignancies who are undergoing chemotherapy.

The above evaluation was triggered by data originating from recent clinical trials showing unexplained excess mortality in oncological patients with anaemia treated with epoetins. Additionally, the results of two studies and one meta-analysis that have recently been published suggest that patients with chronic renal failure treated with epoetins for anaemia, in order to reach relatively high haemoglobin levels, might be at increased risk of cardiovascular mortality and morbidity.

The benefit of these medicines is still greater than their risk, but the following changes to their SPCs have been recommended:

- Change to the *Therapeutic indications* section – epoetins should only be used for the treatment of anaemia **in case the patients have symptoms**.
- Change to the *Posology and route of administration* section – an interval of target haemoglobin levels is set for all epoetins between 10g/dl and 12 g/dl, with a warning **against increasing those levels to concentrations higher than 12 g/dl**.
- Change to the *Special warnings and precautions for use section* – information on the results of trials showing unexplained small excess mortality in association with high target haemoglobin concentration values. No significant benefit has been demonstrated associated with the administration of epoetins to increase haemoglobin above the levels needed to control the symptoms of anaemia and to prevent a blood transfusion.
- Change to the *Pharmacodynamic properties* section – new data from the results of clinical trials showing significant **excess mortality** in patients with various types of cancer and anaemia treated with epoetins versus in those not treated with epoetins.

Health professionals should use epoetins strictly according to the SPC information regarding indications and dosage.

For further information please go to the following EMEA Web address:
www.emea.europa.eu/pdfs/human/press/pus/49618807en.pdf

## Rosiglitazone and Pioglitazone: risk-benefit still positive

On concluding a safety review of thiazolidinediones (rosiglitazone and pioglitazone), EMEA has confirmed that the benefits of these antidiabetic medicines are still superior to the risks associated with their use within their approved indications.

This review was carried out within the scope of the continuing safety monitoring of these medicines and following on new data regarding undesirable effects, which included information on the risk of bone fractures in females and, in the case of patients exposed to rosiglitazone, a possible additional risk of cardiovascular ischaemic disease.

From the available data it has been concluded that the benefits of rosiglitazone and pioglitazone for the treatment of type 2 diabetes are still higher than the attending risks. However, prescribing information for rosiglitazone will be updated in order to include a **warning concerning patients with ischaemic heart disease**. This medicine can only be administered under these circumstances provided the patient's individual risk profile has been assessed appropriately. Additionally, rosiglitazone should **only exceptionally** be administered in association **with insulin**, and under **strict surveillance**. Regarding medicinal products containing pioglitazone, no changes have been decided at this stage.

## Varenicline: beware of depressive symptoms

Champix® (varenicicline) tablets is indicated for helping adults to quit smoking. It was authorised in the European Union in September 2006 and is currently being marketed in several countries.

EMEA has been monitoring the safety of this medicinal product since its authorisation in the EU. It is a pharmacovigilance routine to periodically analyse all adverse reactions reported. In July, October and November 2007 the reported cases of suicide and suicidal ideation were reviewed.

Safety information regarding Champix® is going to be updated to warn prescribers and patients about cases of depression reported in patients trying to quit smoking with the help of varenicicline. Depressive symptoms may include suicidal ideation and attempted suicide.

Recommendations:

* Physicians should keep in mind that trying to quit smoking, with or without pharmacological therapy, has been associated with the **exacerbation of underlying psychiatric conditions** (depression, for instance), and should therefore appropriately advise and follow up on their patients for **symptoms of depression**.
* Patients being treated with Champix® who develop **suicidal ideation** should discontinue their treatment and see their doctor immediately.

## Dopaminergic agonists: psychiatric disorders

Dopaminergic agonists are indicated for the symptomatic treatment of Parkinson's disease, both as monotherapy and in association with levodopa. The following active ingredients belong to this pharmacotherapeutic group: levodopa (in association with carbidopa, benserazide or entacapone), apomorfine, bromocriptine, pergolide, piribedil, pramipexole, rotigotine and ropinirole.

The European Pharmacovigilance Working Party has evaluated the relation between these medicinal products and the possible occurrence of psychiatric disorders such as **pathologic gambling, increased libido, and hypersexuality**. A time relationship was found between the administration of the medicine and the occurrence of the above symptoms. Furthermore, the effects seem to be **dose dependent**. Most patients recovered following treatment discontinuation.

Within this context, INFARMED has asked that the SPCs and Information Leaflets be altered in order to include information on the possibility of occurrence of these adverse reactions.

# Medicines withdrawn

**Cough medicines containing Clobutinol.** The medicinal products containing clobutinol (trademark name Silomat®), indicated for the short-term treatment of non-productive cough, have been withdrawn from the national market on request from the Marketing Authorisation Holder in September 2007. This request was based on the preliminary results of a recent clinical trial pointing to the association of clobutinol with adverse cardiac effects. In fact, EMEA has concluded that the use of clobutinol is associated with a **risk of QT interval prolongation**, which is on its turn potentially associated with heart rhythm disturbances, especially when used in high doses. Since clobutinol is used for treating a common symptom for which there are therapeutic alternatives available, EMEA has considered that the medicine's benefits do not outweigh its risks. **(Madalena Arriegas)**

**Lumiracoxib.** Lumiracoxib is a non-steroidal antiinflammatory agent belonging to the class of selective cox-2 (cyclooxygenase-2) inhibitors, also known as coxibs. It was being marketd in Portugal with the trademark name of Prexige®, indicated for the symptomatic relief of hip and knee osteoarthritis. In December 2007, EMEA concluded a safety information review on **undesirable liver effects**, which indicated that the risks associated with lumiracoxib outweighed its benefits. The SPC had already been changed once before to include a contraindication in patients with potential hepatic problems and the need for regular liver function monitoring. Serious adverse hepatic reactions continued to be reported however, and EMEA considered that the measures proposed by the Marketing Authorisation Holder to reduce that risk did not adequately ensure patient safety.

**Aprotinin.** Aprotinin is a medicine for hospital use indicated for reducing blood loss and blood transfusions in at-risk patients submitted to cardiopulmonary bypass during coronary graft bypass surgery. EMEA concluded in November 2007 that the risks arising from the use of this medicine outweigh its benefits, based on recent and preliminary results of the BART study, which pointed to **increased mortality** in patients who received aprotinin. As a consequence, the suspension of the MA of medicinal products aprotinin for systemic use (Trasylol® and Trasynin®) was recommended. Physicians should assess the need for antifibrinolytic therapy for the prevention of blood loss during bypass heart surgery, and use other medicines with the same therapeutic indication if necessary. Further information can be found on the EMEA website at:
http://www.emea.europa.eu/pdfs/human/press/pr/53467807en.pd.

# 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)

# Medicinal Plants from A to Z
## described adverse reactions

- **Ginkgo** *(Ginkgo biloba)*
  - headache, dizziness
  - palpitations
  - skin and GI reactions

*N.º of Medline citations: 12*

Main uses described: circulatory insufficiency, tinnitus, anxiety/stress, memory deficits

- **Ginseng** *(Panax ginseng)*
  - irritability, anxiety
  - hypoglycaemia
  - diffuse breast nodularity, vaginal bleeding
  - possible interaction with warfarin (decreased antocoagulant effect) and with loop diuretics (antagonism)

*N.º of Medline citations: 14*

Main uses described: immunomodulator, neurologic, cardiovascular, endocrine modulator

- **Guarana** *(Paullinia cupana Kunth)*
  - irritability, anxiety, insomnia, caffeinic effects
  - potentiation of seizures in epileptics (?)
  - contraindicated in pregnancy and lactation

*N.º of Medline citations: 6*

Main uses described: physical and cognitive stimulant, weight loss, antiflatulent, antidiarrhoeal

- **Witch hazel** *(Hamamelis virginiana)*
  - nausea, vomiting, constipation (if ingested)
  - liver toxicity (if excessive tannin absorption)
  - internal use contraindicated

*N.º of Medline citations: 3*

Main uses described: adstringent, haemostatic

- **Hibiscus** *(Hibiscus sabdariffa)*

- decreased effectiveness of antimalarial prophylaxis with chloroquine

*N.º of Medline citations: 5*

Main uses described: diuretic (hipotensor), laxative, antispasmodic, emollient; irritative symptoms of airways

*NB1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. The fact that the therapeutic uses are mentioned here does not mean that they are approved or in any way condoned by this publication.*
*NB2. 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: "side effects", "toxicity in humans", "adverse reactions".*