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From the Editor

Medicines accorded additional monitoring status in Europe will soon start to be graphically highlighted by a specific symbol (a black triangle) printed in their information documents. The underlying concept is that the safety profile of medicines is highly dynamic, which is not always easily comprehended by the public at large and even by health professionals themselves.

A good example of this is the occurrence of adverse reactions which are very rare and/or arise from the use of medicines in complex clinical contexts which cannot be thoroughly replicated in pre-marketing studies. Often they can only be detected following prolonged use of the medicines under non-experimental, real-life conditions.

The current issue of the Boletim includes additionally: changes in the indications of codeine in children, oral ketoconazole, "chronic" use of metoclopramide, ergot derivatives, and various medicines of parentheral use (iron, ambroxol).

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**
- **AND**

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The Black Triangle

When medicines begin to be marketed, they go on to be used by a broader and more diverse group of patients than what had been the case during the pre-marketing study phase. Moreover, patients may present with varying comorbidity and may be taking several other medicines simultaneously. Rarer secondary effects may occur only after long-standing use of the medicine by a great number of patients, which represents a much more far-reaching and diverse exposure than that which is feasible during pre-marketing research. Is is therefore essential that the safety of medicines keep being monitored thorughout its use in daily clinical practice.

In fact, continuing data collection is undertaken from the moment the medicinal product is placed in the market. European authorities conduct comprehensive data monitoring to ensure that the drug's benefits go on outweighing its risks.

Basically the same monitoring methods are utilized within the whole of the European Union (EU). This allows the different authorities to share information collected in each country, and create a vast set of data to be used for decision-making and, whenever necessary, for ensuring the safety of individuals. To that end recommendations for patients and health professionals may be issued or even, when relevant, restrictions of use may be imposed.

The EU has introduced new regulations which allow **medicines more intensively monitored** by authorities to be easily identified. These medicines are classified as being subject to "**additional monitoring**" and present an inverted triangle in the Information Leaflet and SPC, together with an explanatory statement:

▼ **This medicinal product is subjected to additional monitoring**

The black triangle will be used by every EU member state and will mean that for instance because a product is novel the market

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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

INDEX CARD | **Director:** Alexandra Pego **Editor:** Rui Pombal **Assistant Editor:** Leonor Nogueira **Contributors:** Ana Araújo, Catarina Fernandes Costa, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Inês Clérigo, Joana Oliveira, Leonor Nogueira Guerra, Magda Pedro, Margarida Guimarães, Pedro Marques Silva, Teresa Santos Dias **Publishing Assistant:** Inocência Pinto **Advisory Board:** Conselho Directivo do INFARMED, I.P.; Comissão de Avaliação de Medicamentos **Publisher:** INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P., Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa, Tel.: 217 987 316, correio electrónico: infarmed@infarmed.pt **Design and production:** Letras & Sinais, Comunicação e Imagem, Lda. **Legal Deposit:** 115 099/97 **ISSN:** 0873-7118

The Black Triangle

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or there are only limited data on long-term use there is less information available. **It does not mean that the medicinal product is associated with an unfavourable risk-benetit ratio.**

Additional monitoring status will be applied in the following cases:

- **New active** ingredient authorized in the EU after 1 January **2011**.
- **Biological** medicinal products, such as vacines or plasma-derived products, with which there is **little post-marketing experience**.
- **Conditional authorization** (whenever the MA Holder is obliged to provide further safety data) or authorization under **exceptional circumstances** (whenever there are specific reasons that exempt the MA Holder from providing relevant data)
- The MA Holder is bound to conduct **further studies**, for example to furnish additional data on long-term use or on some rare side effect observed during the clinical trial phase.

There are also **other** medicines which may be subject to additional monitoring as decided by the PRAC at EMA.

The European list of medicinal products subjected to additional monitoring began to be published by EMA in April 2013. This list is reviewed by PRAC on a monthly basis and can be found at:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142453.pdf .

Any medicine may be entered in the list at the time of its initial approval or at any time throughout its life cycle. Additional monitoring goes on **for five years** or until the PRAC decides to remove the medicine from the list.

The black triangle will be included in the Information Leaflets of applicable medicines from the **last quarter of 2013**. It will not appear on the outer packaging, nor in the labels. It will facilitate quick identification of medicines subjected to additional monitoring. It is especially important to report any suspected adverse reactions observed with the earmarked products. In Portugal, reporting can be done online at the Portal RAM (*ADR Portal*) – see box below.

Fátima Hergy, Cristina Mousinho

Online reporting of adverse drug reactions by health professionals and patients

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Codeine: Restrictions of use for pain relief in Children

PRAC has agreed on a set of recommendations for medicines containing codeine used for pain relief in children, following cases of **respiratory depression in children who are ultra-rapid CYP2D6 metabolizers**. A very small number of fatal or life-threatening cases (none of which in Portugal) has been reported in children receiving codeine after having their tonsils or adenoids surgically removed.

Human metabolism converts codeine into morphine via the CYP2D6 enzyme. In some individuals – called ultra-rapid CYP2D6 metabolizers - this enzyme's activity is increased. Codeine conversion therefore takes place at faaster than normal rate, increasing circulating morphine levels and thus the probability of toxicity in the form of respiratory depression.

General opioid toxicity manifestations include confusion, somnolence, superficial breathing, small pupils, nausea, vomiting, constipation and loss of appetite. In serious cases circulatory and respiratory depression may occur, which can be life threatening and very rarely fatal.

According to the SPC of codeine, an estimate of the prevalence of ultra-rapid metabolizers in some populations is summed up in the following table.

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian in general	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

The PRAC recommends that a set of risk minimization measures be implemented in order to ensure that codeine-containing medicinal products will be used in the relief of pain in children only when benefits outweigh risks.

The new prescription and utilization **recommendations** are as follows:

- Codeine is indicated in children older than 12 years for the treatment of acute (short-term) and moderate pain which **cannot relieved by other analgesics** such as paracetamol and ibuprofen (in isolation).
- It should be used in the **lowest effective dose** and for the shortest possible period of time. It may be increased up to 4 times a day, at **intervals no shorter than 6 hours**. The **maximum daily dose** of codeine should not be higher than **240 mg**.
- Codeine is **contraindicated** in children (younger than18 years) subjected to surgical removal of **tonsils or adenoids**, in ultra-rapid cytochrome CYP2D6 **metabolizers**, and in **breastfeeding** women.
- The use of codeine is not recommended in children whose **respiratory function may be compromised** (e.g., neuromuscular conditions, severe cardiac or respiratory conditions, upper or lower respiratory infections, multiple trauma, or extensive surgical procedures), since they may worsen the manifestations of morphine toxicity.

The SPCs of codeine-containing medicines are going to be updated in accordance with the above.

Joana Oliveira

Diclofenac: Minimization of Cardiovascular Risk

The safety of non-steroidal anti-inflammatory agents (NSAIDs) has been the object of monitoring by the EU authorities. Safety reviews undertaken to date confirm that this class of medicinal products is associated with a slight increase in the risk of arterial thromboembolic events which, in some cases, may manifest as myocardial infarction or cerebrovascular accidents, especially when high doses are used for prolonged periods of time.

The SPCs and Information Leaflets of NSAIDs warn about the above risks and recommend that these medicines be used in the lowest effective dose and solely during the period of time required for symptom control.

Diclofenac is an NSAID used for the relief of pain and inflammation, namely at bone joint level. The PRAC at EMA has concluded that the effects of diclofenac in the heart and circulation are similar to those of another NSAID class, that of COX-2 selective inhibitors, in situations where the former is used systemically (capsules, tablets or solution for injection) and especially when used in high doses (150 mg qd) and in prolonged treatments.

The above-mentioned safety review concluded once more that diclofenac-containing medicines are effective in reducing inflammation and pain, and that their **benefits outweigh their risks**. However, given that the cardiovascular risk associated with systemic administration seems to be similar to that of COX-2 selective inhibitors, the same cardiovascular risk minimization measures should be applied. Thus, EMA and Infarmed recommend:

- The use of diclofenac is **contraindicated** in patients with established congestive (New York Heart Association class II-IV) cardiac failure, ischaemic cardiopathy, peripheral arterial disease, or cerebrovascular disease.
- Patients with significant **risk factors** for **cardiovascular** events (e.g., hypertension, hyperlipaemia, diabetes mellitus or smoking) should only receive diclofenac after appropriate **assessment**.
- Diclofenac should be used in the **smallest effective daily dose** and for the **shortest time possible**.
- The need for symptom control and the patient's response to therapy should be periodically **re-evaluated**.

Margarida Guimarães

IV Iron: Minimization of Allergy Risk

Products containing iron for intravenous (IV) administration are indicated for the treatment of iron deficiency and anaemia only when the oral route cannot be used or is not effective. The IV route has an associated **low risk of allergic reactions.** However, the latter may be fatal if not rapidly treated. Risk of **hypersensitivity** is greater in patients with a history of allergy, with immunological or inflammatory conditions, a history of severe asthma, eczema or atopy.

In Portugal, authorized iron-containing products for IV administration include as active ingredients ferric hydroxide sucrose complex and iron-dextran complex. Following a safety review of iron-containing medicines, EMA has concluded that **benefits outweigh** risks provided measures are taken to minimize the risk of occurrence of allergic reactions.

Recommendations:

- These medicines should only be given at **facilities** with resuscitation capabilities and by trained **health professionals**.
- **Patients** should be **informed** about the risk and seriousness of hypersensitivity reactions, as well as about the need to seek medical assistance should they supervene.
- The use of a **test-dose** to check for patient's hypersensitivity is **not** recommended.
- Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions for at least **30 minutes** after each administration.
- **Every dose** of iron given intravenously should be **monitored**, even when previous administrations have been well tolerated.
- IV iron should not be given during **pregnancy**. If absolutely necessary, therapy should be limited to the second or third terms, and provided the benefits surpass potential serious risks, such as those of foetal distress or anoxia.
- In case a hypersensitivity reaction occurs, iron administration should be immediately discontinued and adequate **treatment** started.

Margarida Guimarães

Mucosolvan 15mg/2ml (ambroxol chlorhidrate for injection): Changes in the Dilution recommendations

Mucosolvan 15mg/2ml Solução Injetável (ambroxol chlorhydrate for injection) is indicated to improve the production of lung surfactant in newborns, including premature babies, with respiratory distress syndrome. It can be given in a drip perfusion after dilution in saline or in Ringer's solution. No other solution for dilution should be used, namely 5% glucose or 5% levulose solutions.

In fact, compatibility studies of Mucosolvan 15mg/2ml Solução injectável both in saline and in Ringer's have demonstrated these dilutions to be stable. On the other hand, recent stability studies have shown that, when the medicine is diluted in a 5% glucose solution, an impurity (N-A 873 CL) forms which results from a chemical reaction between ambroxol chlorhydrate and formaldehyde, traces of the latter being usually found in 5% glucose solutions. It has not been possible to study the stability of a dilution of this medicine in a 5% levulose solution. Therefore, given the lack of compatibility data, this dilution is not recommended.

The medicine's SPC section 4.2 *Posology and method of administration* has been reviewed and updated accordingly.

Teresa Santos Dias

Metoclopramide: Change in recommendations of Use

On account of persisting concerns about the effectiveness and safety of metoclopramide, EMA has undertaken a safety review which included data from published studies and metaanalyses on the efficacy of metoclopramide, as well an analysis of suspected cases of ADRs.

The review confirmed the **already known risks** of neurological effects such as short-term extrapyramidal disorders (involuntary muscle movements that may involve the head and neck) and tardive dyskinesia (uncontrollable movements such as grimaces and spasms). The risk of **short-term neurological** effects is higher in **children**, whereas **tardive dyskinesia** is more frequently reported in the **elderly**. Risk increases with **higher doses or prolonged treatments**. Cases of serious **cardiac and circulatory** side effects have also been reported, especially following **parenteral administration**.

In what regards the efficacy of metoclopramide in **chronic conditions**, its benefits no longer outweigh the attending risks of side effects. Metoclopramide should therefore **not be used** to treat long-standing disorders caused by gastric emptying delay, indigestion, reflux or heartburn. Additionally, there is no evidence to justify the use of metoclopramide as an adjuvant in radiological or surgical procedures.

Accordingly, the **therapeutic indications** of metoclopramide are **now limited to** the relief of **nausea and vomiting** of various origins (e.g., post-chemo or radiotherapy, post-surgery, or migraine-associated emesis), and to **isolated and short-duration cases of gastrointestinal motility disorders**.

The following are the updated recommendations for use of metoclopramide:

- Duration of treatment with metoclopramide should be limited to a **maximum of 5 days** (acute conditions).
- In **adults**, metoclopramide is **still indicated for** the prevention of post-operative nausea and vomiting (PONV), nausea and vomiting induced by chemotherapy and late (not acute) chemotherapy-induced emesis, as well as for the symptomatic treatment of nausea and vomiting including when associated with migraine. In the latter case, metoclopramide may also be used to increase the absorption of oral analgesics.
- In **children older than 1 year**, metoclopramide should only be used as second-line treatment for the prevention of late chemotherapy-induced nausea and vomiting and for the treatment of PONV.
- In **children younger than 1 year**, the use of metoclopramide is **contraindicated**.
- In adults and children, the **maximum daily dose is 0.5 mg per kilogram** of body weight:
  - Adults – the usual dose is 10 mg up to three times a day.
  - Children – the recomended dose is between 0.1 and 0.15 mg per kg of body weight, up to three times a day.
- The **oral liquid formulations** have been associated with cases of overdose in children. For this reason, packages with dosing higher than 1 mg/ml are going to be withdrawn from the EU market; the formulations which are keeping its authorization status should be administered by using an **oral dosing syringe** to ensure dose accuracy.
- Both the intravenous formulations at concentrations **higher than 5 mg/ml** and the **20 mg suppositories** will also be **withdrawn**.
- The intravenous formulations which go on being authorized should be administered as a **slow bolus** (at least three minutes) in order to decrease the risk of adverse reactions.
- In **populations** at higher risk of adverse cardiovascular reactions (the elderly, patients with cardiac conduction changes, non-corrected electrolyte imbalance, bardycardia, or patients on medicines known to prolong the QT interval) **great care** should be exerted when using metoclopramide, especially via the intravenous route.

These recommendations are going to be included in the SPCs of metoclopramide-containing medicines, and the treatment should be reviewed by the doctor accordingly in the following routine medical appointment.

Joana Oliveira

ORAL Ketoconazole: Suspension recommended

The Committee for Human Medicinal Products (CHMP) at EMA has recommended that the MA of medicinal products containing ketoconazole for **oral administration** be suspended, following conclusive evidence that the **risk of liver injury** is higher than the benefits in the treatment of fungal infections. The CHMP opinion will be sent to the European Commission (EC) for a binding decision.

A Europe-wide review of safety data regarding oral ketoconazole was initially triggered following the suspension of this product in France. The CHMP has concluded that, although liver injury such as hepatitis, is a known adverse effect of antifungals in general, the incidence and seriousness of these reactions were higher for oral ketoconazole in comparison with other antifungals.[1] Liver injury reports correspond to the beginning of treatment in the recommended doses (200 mg), and no measures liable to adequately reduce their risk have been identified. The reports included cases of hepatitis, cirrhosis and hepatic failure, which required liver transplantation or were fatal. The clinical benefits of oral ketoconazole are not well known, since data on its efficacy are limited. On the other hand, there are alternative therapies available.

In Portugal, only one orally administered, ketoconazole-containing medicinal product is authorized and marketed: Nizale, 200 mg tablets. Given the above risk-benefit assessment, EMA and Infarmed recommend the following:

Health professionals:

- Therapy with oral ketoconazole should be reviewed and, if possible, an alternative treatment started.
- Systemic absorption of ketoconazole from **topical** use products is very low; therefore the latter can **continue to be used** within the approved indications.
- Whenever presented with a prescription for oral ketoconazole, pharmacists should recommend that patients make an appointment with the doctor for treatment review.

Patients:

- *Should you be taking an orally administered medicine containing ketoconazole for the treatment of fungal infections, bring this matter up with your doctor in your next appointment, so an alternative prescription may be considered.*
- *In case you are using other products containing ketoconazole, such as creams, ointments or shampoos, you should not interrupt your treatment, since the amount of ketoconazole absorbed is very low.*

Catarina Costa

[1] Garcia Rodriguez *et al*. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. Br J Clin Pharmacol 1999; 48(6):847-852.

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