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From the Director

"A climate of openness is the fundamental key to effective communication. In a secretive environment, information would never be taken at face value or be perceived as credible."

"The Verona Initiative" 1997

2005 is the Boletim's ninth anniversary year. It is the obligation of all those of us who devote their attention to studying and monitoring the safety of medicines to handle with great care all the information we generate and convey. This is all the more relevant in view of the current background of growing complexity and scope of pharmacological therapy, making information credibility and transparency an ever present demand. It is widely known that the media also play a fundamental role in communicating about issues regarding the use of medicines. They often produce the first wave of information reaching the public and even health professionals. This information unfortunately not always has firm scientific grounding.

Our foremost goal is to produce quality information which may contribute towards minimising the risk of its being disseminated in confusing or incorrect terms. We want to have such an influence on the use of medicines that every single time they may be used in the safest and most effective possible way. Communicating is not about one party talking and the other party listening. Effective communication is always an interactive experience involving all the various parties.

The Boletim seems to be well established within the health professionals' community, not only in Portugal but also in Portuguese speaking countries elsewhere. It is also well known by its European partners in the field. We aim to come as close as possible to our readership, and to provide them with a service that meet their expectations and which they can use in their daily professional lives. It is extremely important for us that our readers and all those interested should tell us of their opinions regarding the kind of information we produce, as well us give their suggestions towards helping this bulletin to keep on evolving on a path of accuracy and quality.

Regina Carmona
Director, INFARMED Pharmacovigilance Dept

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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Safety restriction for COX-2 inhibitors:

• **Contraindicated** in patients with **cardiac disease or stroke.** Etoricoxib is additionally contraindicated in patients with uncontrolled arterial hypertension.

• **Special precaution** when prescribing in individuals with **risk factors for coronary disease,** such as high blood pressure, hyperlipidaemia, diabetes, and smoking, as well as in patients with **peripheral arterial vascular disease.**

• Use the **lowest effective dose** for the **shortest possible** period of time.

NB: For further details see Bols N. 3 and 4, 2004, and go to www.infarmed.pt ***or*** www.emea.eu.int

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Portugal em Acção

Safety of Antidepressants in Children and Adolescents

The CHMP reassessed the issue of potential suicidal behaviour in children and adolescents undergoing therapy with two classes of antidepressants: **Selective Serotonin Re-Uptake Inhibitors (SSRIs), and Serotonin and Norepinephrine Re-Uptake Inhibitors (SNRIs).** The active ingredients approved in Portugal which were re-evaluated were: **citalopram, duloxetine, escitalopram, fluoxetine, mianserine, milnacipram, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine.**

It has been concluded that **suicide**-related behaviour (attempted suicide and suicide ideation), and **hostility** (predominantly aggressiveness, opposition behaviour and anger) were seen much more frequently in clinical trials in children and adolescents who had been taking these antidepressants, when compared to those taking placebo. Within this context, using these medicines in children and adolescents is not recommended, the **approved indications** excepted. Some of these drugs are indeed authorised for paediatric use for the treatment of obsessive-compulsive disorders. Atomoxetine (although not marketed in this country) is additionally approved for the treatment of attention deficit/hyperactivity disorder.

The physician may however at times prescribe these medicines to children or adolescents in well **individualised cases,** for the treatment of anxiety or depression. The CHMP recommends that under those circumstances patients be **strictly monitored** regarding the appearance of suicidal behaviour, self-aggressiveness or hostility, **especially at the onset of therapy.**

Whenever therapy with this class of medicines is to be interrupted, its **dosage should be gradually tapered** for a period of several weeks or months, in order to prevent withdrawal reactions (e.g.: dizziness, sensorial disorders, sleep disturbances, anxiety, headache).

NB: See Bol. n. 4, 2004.

HIV/TB Co-Infection Rifampin Contraindicated with Saquinavir/Ritonavir

Tuberculosis is currently responsible for the greater number of deaths among HIV-positive and AIDS patients. Although HIV/TB co-infection is becoming ever more frequent, data on concomitant therapy are still limited, mainly in what concerns interaction profiles. First-line antibacillary agents for TB are isoniazide, pyrazinamide, rifampin, and ethambutol. Concerning their concomitant use with antiretroviral agents, both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) may inhibit or induce cytochrome P450 (namely CYP3A4). Thus the use of rifampin has become a major problem in that it speeds up PI metabolism, causing the latter to go down to subtherapeutic levels. PIs on their turn slow down rifampin metabolism, causing their blood serum levels to rise and consequently their toxicity to increase.

Up until now rifampin had been included in the therapeutic regime, since it is an essential antibacillary agent. Ritonavir had been used to potentiate PIs. However, new data have surfaced this year which have demonstrated that rifampin should not be used in patients who are on combined antiretroviral therapy including the saquinavir/ritonavir association. In one clinical pharmacology study, iatrogenic hepatitis was observed in healthy volunteers who had been exposed to rifampin (600 mg daily) in association with 100 mg ritonavir and 1000 mg saquinavir, twice daily.

These new data have led to the **SPCs to be altered** so that the saquinavir/ritonavir + rifampin association is contraindicated, and a warning is made concerning **the hepatotoxic potential of their combined** use. Should changes to the antiretroviral therapy not be at all possible, then rifabutin (also a CYP430-inducer, though less potently so) may also be considered as an alternative to rifampin.

Isabel Brito Afonso

- CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR 1998; 47 (no. RR-20).
- Valadas E. Tuberculose e infecção por VIH. Biblioteca da SIDA. Lisboa: Penmanyer Portugal; 2005. p: 21-6.
- Veldkamp A, et al. Ritonavir enables combined therapy with rifampin and saquinavir. Cli Infect Dis 1999; 29:1586.

Pimecrolimus and Tacrolimus under review

Elidel® (pimecrolimus) and Protopic® (tacrolimus) are topically applied immunosupressive agents which are indicated for the treatment of atopic dermatitis (eczema). According to the results of studies conducted **in animals receiving excessive doses,** and to cases received through **spontaneous reports,** these medicines may be associated with an added risk of occurrence of malignant neoplasms. EMEA started a review in April of all topically applied immunosupressive medicines containing pimecrolimus and tacrolimus taking into account their potential risk. As soon as this review is concluded INFARMED will disseminate all the relevant information.

Phenylpropanolamine-containing medicines suspended

Phenylpropanolamine is a sympathomimetic agent which is used in association in medicines for the treatment of flu and head cold associated symptoms of nose congestion. In Portugal, there are three authorised medicines containing phenylpropanolamine: **Rinogan®** and **Ornade Spansule®,** both requiring medical prescription, and containing 75 mg phenylpropanolamine (in association with chlorphenamine), and **Antigripine®,** which contains 12 mg phenylpropanolamine (among other active ingredients) and which is classified as an over the counter medication.

Following reports of serious ADRs worldwide, including **haemorrhagic stroke,** in which phenylpropanolamine's involvement could not be excluded, INFARMED has decided to promote a reassessment of the risk-benefit ratio of this active ingredient, which was deemed unfavourable. Considering the safety information available on phenylpropanolamine, the existence of marketed alternatives, and **although in Portugal no serious adverse effects of phenylpropanolamine have been detected,** all medicines containing this ingredient have been suspended for ninety days.

Isabel Brito Afonso

Isotretinoin
pregnancy prevention programme

The European Commission has decided to harmonise the information contained in the SPC of Roaccutan®, whose active ingredient is isotretinoin. INFARMED has implemented this decision for all medicines containing isotretinoin currently in the national market.

Isotretinoin is a retinoid, vitamin A derived substance which is used for the systemic treatment of acne. Like other retinoids, isotretinoin is teratogenic and is contraindicated during pregnancy. Taking into account its teratogenic risk, as well as other serious undesirable effects, isotretinoin now has the following indication: **"manifestations of severe acne (such as cystic acne, acne conglobata, or disfiguring acne) which are resistant to adequate periods of standard treatment with systemic antibacterial agents and topical therapy."**

Regarding safety, the information that should be included in the SPC on recommendations for women of childbearing potential has been harmonised based on a pregnancy prevention programme (PPP). Isotretinoin is therefore **contraindicated in women of childbearing potential, even when not sexually active, unless** the patient:

1. has **acne that is resistant** to conventional therapy;
2. understands the **teratogenic risk** associated with isotretinoin;
3. understands the need for **monthly medical follow-up;**
4. understands and accepts to use **effective, uninterrupted contraception,** for one month before, during and as late as one month after treatment; a contraceptive method (preferably two) should be used including one barrier device;
5. **effectively uses contraception,** even when amenorrhoeic;
6. is **informed and understands** the consequences of pregnancy, and the need to promptly see a doctor in case pregnancy is suspected;
7. accepts to undergo **monthly pregnancy testing,** before, during, and until as late as 5 weeks after treatment finishes;
8. **explicitly declares** that she has understood every measure and potential harm associated with isotretinoin.

Isotretinoin should only be prescribed by physicians with **experience in the use of systemic retinoids** for the treatment of severe acne, and who are aware of the risks of isotretinoin therapy, as well as of its monitoring requirements.

Since prescription for women of childbearing potential is **limited to 30 days of treatment and is valid for 7 days only,** the pharmacist should be informed about the PPP and pay special care whenever dispensing isotretinoin to women of childbearing potential. To have her prescription renewed the woman has to go and see a physician again and get a new pregnancy test.

Other recommendations:

- Every patient should be instructed so as not to give this drug to **other persons,** especially female, **nor to donate blood during and until as late as one month after** treatment is finished.
- In case **pregnancy is suspected** the woman should discontinue her therapy and see her doctor immediately.
- In case of **pregnancy,** the physician should discontinue therapy, refer the patient to another physician specialised or experienced in teratology, and immediately report it to the authorities and the MA Holder.
- **Male patients:** Available data suggest that maternal exposure to semen and seminal fluids of men being treated with isotretinoin does not warrant concern of isotretinoin-associated teratogenic effects.

Companies marketing isotretinoin are committed to:

- not furnishing free samples;
- reporting on the implementation of the PPP, as well as on all cases of foetal exposure, every six months for the first two years, annually thereafter;
- notifying the authorities within 15 days in case of pregnancy;
- elaborating and providing physicians, pharmacists and patients with information, by means of the following INFARMED approved brochures:

  - ***Prescribing isotretinoin: physician's guide.***
  - ***Dispensing isotretinoin: pharmacist's guide.***
  - ***Female patient prescription control list.***
  - ***Patient information brochure.***
  - ***Information brochure on contraception.***
  - ***Informed consent form to be signed by the female patient.***

Commission Decision C(2003)3929, 17 Oct 2003

Alexandra Pêgo

Medicinal Herbs from A to Z
adverse reactions described in the literature

- **Artichoke**
  - contact dermatitis
- **Alfafa**
  - interference in antibody synthesis (children, elderly, immunodeficient patients)?
  - pancytopoenia
  - cases of S. enterica, E. coli and Listeria infection through contaminated seeds or sprouts
- **Aloe (topical)**
  - burn sensation on application on abraded skin
  - contact dermatitis (aloe arborescens)
- **Aloe (systemic)**
  - diarrhoea, colic

Antiepileptics in general and valproic acid *increased risk of congenital malformations*

The SPCs and Information Leaflets of all antiepileptic medicines shall contain the following information:

- Every woman of childbearing age (potential) should receive **specialist medical counselling before treatment is started,** due to an increased risk of congenital malformations.
- Antiepileptic therapy should be **reassessed whenever the woman wishes to become pregnant.**
- **The risk of congenital malformations is 2 to 3 times greater** in the offspring of women taking antiepileptic drugs. The most frequent malformations affect the lips and oral cavity, the cardiovascular system, and the neural tube.
- Multidrug antiepileptic regimes may be associated with a higher risk for congenital malformations when compared to single agent therapy**. Whenever possible a single antiepileptic regime** should be used.
- Treatment with antiepileptics **should not be suddenly discontinued,** since the risk of seizures may be increased with serious consequences for the mother and/or the foetus.

Special issues regarding medicines containing **valproic acid:**

- Valproic acid is the treatment of choice for patients with certain types of epilepsy, such as generalised epilepsy with or without myoclonus and/or photosensitivity. In partial epilepsy valproic acid should only be used in case of failure of other therapeutic regimes.
- Increased incidence of congenital malformations (including **hypospadias, facial dysmorphism, and limb malformations)** has been reported in the offspring of epileptic women treated with valproic acid, when compared to other pregnant women on different antiepileptic regimes.
- During pregnancy, valproic acid should be prescribed as **monotherapy,** in divided doses, or preferably in **sustained-release preparations,** always at the lowest possible dose.
- High total daily doses or total individual doses are associated with unfavourable pregnancy outcomes. Evidence points to an association between elevated serum level peaks and elevated individual doses, and neural tube defects. The incidence of neural tube defects in pregnant women medicated with valproic acid is 1 to 2%. The incidence of **neural tube defects** increases with **higher daily doses,** especially from 1000 mg per day.
- The use of **folate supplementation since before pregnancy** may reduce the incidence of neural tube defects in children born to high risk mothers. The recommended daily dose of folic acid is 5 mg per day starting at the pregnancy planning stage.
- In **new-borns** whose mothers took valproic acid during pregnancy, **very rare cases of haemorrhagic diathesis** have been reported. This syndrome is related to hypofibrinogenaemia. Cases of afibrinogenaemia, a potentially fatal condition, have also been reported. All new-borns should be tested for **coagulation, blood platelet count, and plasma levels of fibrinogen.**
- Women on valproic acid who become pregnant should be **regularly monitored throughout their pregnancy** by ultrasonographic means, and other appropriate ancillary tests.
- **There is no evidence that women taking valproic acid should not breastfeed.**

Alexandra Pêgo

- *Wide K, et al. Major malformations in infants exposed to antiepileptic drugs in utero, emphasis on carbamazepine and valproic acid: a nation-wide, population register study. Acta Paedriatr 2004 Feb; 93(2):174-176.*
- *Adab N, et al. Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001 Jan;70(1):15-21*
- *Arpino C, et al. Teratogenic effects of antiepileptic drugs: Use of an international database on malformations and drug exposure (MADRE). Epilepsia 2000;41(11):1436-43*
- *Holmes LB, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001; 344:1132-8*

What should one report?

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

- Causing death
- Putting life at risk
- Causing hospital admission
- Prolonging hospital stay
- Resulting in persistent or significant incapacity
- Suspected congenital anomaly or malformation
- The health professional considers it to be a serious ADR even though it does not meet any of the above criteria

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)