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Editor's Notes

INFARMED has made the Summaries of Products' Characteristics (SPCs) of medicines available through its INFOMED link. As mentioned in this Bulletin's former issue, the INFOMED link can be easily found in the footnote area at INFARMED's homepage. Even those who are not used to surfing the net can confidently use this link:
1st Write http://www.infarmed.pt/ and click on the INFOMED icon at footnote level, or directly key in http://www.infarmed.pt/infomed/inicio.php
2nd Click on "Entrada Livre" (Free Access).
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4th Key in the item you are searching (e.g.: by INN or trademark name).
5th Click on "Pesquisar" (Search) or press "Enter" in your computer's keyboard.
6th You can now see a brief description of the medicinal product. Click on "Detalhes" (Details).
7th More detailed information appears on the screen. If available, click on "RCM" (SPC) to obtain the Summary of the Product's Characteristics, or on "FI" (IL) to access the Information Leaflet. A separate window opens with a pdf file. You can click on Print if desired.
This online search takes an average 30 to 90 seconds, depending on your computer and your internet connection. Have a nice search!

Rui Pombal

What do they stand for?!

ADR	Adverse Drug Reaction
CPMP	European Committee of Proprietary Medicinal Products
EMEA	European Medicines Evaluation 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/reaccoes_adversas/fichas_notificacao/index.html

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COX-2 Inhibitors
review of safety profiles

Following the withdrawal of rofecoxib from the world market, EMEA has been asked by the European Commission to re-evaluate the whole COX-2 inhibitor drug class as a precautionary measure (see former issue of the Boletim). As a consequence, EMEA's scientific committee on medicines for human use (CHMP), in which INFARMED experts also take part, will be reviewing and analysing every aspect of the cardiovascular safety of COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib, parecoxib, and valdecoxib), including thrombotic (e.g.: myocardial infarction and stroke), and cardiac and renal events (e.g.: arterial hypertension, oedema, cardiac failure). This review aims to assess the need for any change to MAs, including the data contained in the SPCs

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Portugal em Acção

and Information Leaflets, and/or for additional studies to be designed and carried out.

For the time being, the information sent to physicians and patients by EMEA on 10th October will stay current. Thus:

• **Patients to whom rofecoxib has been prescribed:** Given a possible risk of serious thrombotic events, the therapeutic regime of these patients must be reviewed taking into account available alternatives.

• **Patients who are on a prescription for another COX-2 inhibitor:** The data included in the latest version of the SPC should be borne in mind, especially regarding warnings and special precautions in patients with a history of cardiovascular disease.

The SPCs of COX-2 inhibitors (centralised procedure) can be obtained (also in Portuguese) from EMEA's online site, included in the EPAR (European public assessment reports) lists at:

Celecoxib:
www.emea.eu.int/humandocs/Humans/EPAR/onsenal/onsenal.htm

Parecoxib
www.emea.eu.int/humandocs/Humans/EPAR/dynastat/dynastat.htm

Valdecoxib
www.emea.eu.int/humandocs/Humans/EPAR/bextra/bextra.htm

Information pertaining to the results of a former referral by EMEA regarding medicines containing celecoxib, etoricoxib, and rofecoxib, and their corresponding SPCs, was made public last June and may be accessed at:
www.emea.eu.int/htms/human/referral/referral.htm

Additional information on this subject is available online at both INFARMED's and EMEA's sites:

Press release from 6th October:
www.infarmed.pt/pt/noticias_eventos/noticias/nt_06_10_2004_2.pdf

Information Circular on Market Withdrawal of Vioxx®, Ceoxx®, and Coxxil®:
www.infarmed.pt/pt/alertas/seguranca/al_30_09_2004.pdf

Statement from EMEA following market withdrawal of Vioxx® (rofecoxib):
www.emea.eu.int/htms/hotpress/d9794904.htm

For any further information:

• INFARMED Medicinal and Health Products Information Centre - the Medicines Green Number +351 800 222 444, or by e-mail centro.informacao@infarmed.pt

• Pharmacovigilance Department, by phone +351 21 798 71 40, or by e-mail farmacovigilancia@infarmed.pt

INFARMED has been following up and acting on this process, namely through its experts working at the CHMP, as well as through its Pharmacovigilance Department and Medicines Evaluation Committee. Further relevant information will be promptly disseminated to health professionals as it is made available.

A Faria Vaz

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

risk of suicidal behaviour in children and adolescents

EMEA's Committee on Medicines for Human Use (CHMP) met on 8th December last to re-examine its opinion issued at the European Commission's request in April 2004 regarding paroxetine. This was triggered by new available information coming from data from observational studies.

The initial conclusion that **paroxetine's risk-benefit ratio remains favourable for the treatment of adult patients** was confirmed. Very close monitoring is recommended in patients with a high risk of suicidal behaviour, namely patients with a known history of suicidal behaviour or ideation prior to treatment, and young adults. CHMP further confirmed the need to change the information on paroxetine, especially regarding the **warnings against potentially suicidal behaviour in children and adolescents**.

Additionally, the European Commission has asked the CHMP to review the data made available by national authorities on other selective serotonin reuptake inhibitors (SSRIs) and on serotonin and norepinephrine reuptake inhibitors (SNRIs), especially in what respects to their use in paediatric populations. Data were reviewed on the following medicines: **atomoxetine, citalopram, duloetine, escitalopram, fluoxetine, fluvoxamine, mianserine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine**. Also for this purpose CHMP set up an ad hoc group of experts which included child psychiatrists. The data analysed included:

- Twenty-eight short-term, randomised, placebo-controlled studies, which had been submitted to European authorities (15 on major depressive disorder, 7 on anxiety disorders, and 6 on attention deficit/hyperactivity disorders (ADHD)), corresponding to over 5,000 patients;
- Eight other randomised, placebo-controlled trials which had been published in medical literature;
- Several observational studies based on the GPRD (UK General Practice Research Database), and ecological studies.
- Data from active control, or from extension, non-controlled studies were left out, in that they could not be compared to placebo.

No cases of death by suicide were reported in any of the clinical trials on children and adolescents.

The studies on **major depressive disorder** consistently showed an increased risk of potentially suicidal behaviour (suicide attempt or suicidal ideation) for every antidepressant drug. A signal of potential risk also arises, although not so markedly, from the studies on **anxiety disorders**, whereas

the studies on **ADHD** did **not** show any increase in suicidal behaviour. The GPRD studies pointed towards some differences among medicines. This was not confirmed however by evidence from the randomised trials.

CHMP considered, based on available evidence, that there is a signal for risk of suicidal behaviour, including suicide attempt and suicidal ideation and/or related behaviours (such as self-aggression, hostility, and emotional lability) in children and adolescents on SSRIs or SNRIs.

Awaiting further investigation at Community level, CHMP informs physicians, patients and healthcare providers of the following:

- In Europe, **SSRI/SNRIs** are not authorised for the treatment of depression and anxiety disorders in **children or adolescents. In general, these medicines should not be used in these age groups, in that clinical studies have shown some risk of increased suicidal behaviour** (namely suicide attempts and suicidal ideation).

- **However**, specific clinical conditions may at times make it necessary to treat those patients with SSRI/SNRIs. In these cases, patients should be **carefully followed up**, so that any manifestation of **suicidal behaviour, self-aggression or hostility** may be detected early on. This is particularly relevant **when therapy is initially started**.

- Therapy should not be discontinued by the patients themselves or their parents without first getting their doctor's advice, due to the risk of **withdrawal symptoms** such as dizziness, sleep disturbance and anxiety. This is especially true for abrupt discontinuation of therapy. In fact, whenever treatment has to be interrupted, gradual dose reduction over several weeks or months is recommended.

Methadone
QT prolongation and tordsade de pointes

Methadone chlorhydrate is a synthetic opioid drug which is given as replacement therapy for heroin addiction. In Portugal this medicine is dispensed to substance addicted patients included in methadone replacement therapy programmes. It has been recently found that this product may cause cardiac rhythm disturbances. Rare cases of QT-interval prolongation and *torsade de pointes* have been reported, especially when methadone is given in **high doses (> 200 mg/day)**. Though rare, these episodes can be serious.

Special care is recommended whenever giving methadone to patients with a known risk of QT prolongation. In these cases an **ECG** should be obtained prior to starting the treatment, as well as before any dosage increments are made. Caution should be exerted therefore when administering methadone to **patients with a history of QT prolongation, advanced heart disease, or who are concomitantly taking other drugs which may cause QT-interval prolongation**.

The metabolism of methadone is mediated by isoenzyme CYP3A4. Simultaneous administration of medicines which inhibit this isoenzyme's activity, such as certain anti-HIV drugs, macrolide antibiotics, cimetidine, and azol antifungals, will lead to decreased methadone clearance. Moreover, the risk of cardiac complications should also be taken into account when simultaneously administering medicines which affect cardiac conduction, or which have a potential to cause electrolyte disturbances.

Patients should be informed and urged to see their doctor in case of symptoms such as dizziness, vertigo, palpitations, breathlessness, or loss of consciousness.

Paula Roque

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Drospirenone + ethinylestradiol
considering the risk of venous thromboembolism

Venous thromboembolism (VTE) is a well-known though very rare adverse reaction to combination oral contraceptive drugs (estrogens + progestagens). There is evidence suggesting that the risk of VTE directly depends on the type of progestagen used. Earlier in 2001 information on this risk was disseminated and included in the SPCs of this class of medicinal product.

The progestagen drospirenone, apart from a progestagenic action, also presents some antiandrogenic properties and mild antimineralocorticoid activity. Since VTE is considered to be a rare event, a possible increased risk of VTE associated with combination oral contraceptives containing drospirenone and ethinylestradiol was not known at the time this medicinal product was first granted Marketing Authorisation.

Current, preliminary data from a UK study (Prescription Event Monitoring – PEM) suggest there might be an increased risk of VTE associated with the drospirenone + ethinylestradiol combination. However this is not a comparative study. Women were evaluated in their first year of use of the drug while it is known beforehand that the risk of VTE is higher during the first year of use of any oral contraceptive agent. An extensive, observational, cohort - therefore comparative – study, which compares women using drospirenone 3 mg + ethinylestradiol 0.03 mg, versus women using combination contraceptives containing levonorgestrel, versus other users of combination contraceptives, is under way. In this trial, which is expected to be concluded by 2006, 52,000 women-years have been evaluated thus far, including 16,000 women-years taking the drospirenone combination agent. The rate of VTE in these users seems to be comparable to that of women on other oral contraceptives. Contrarily to other observational studies, whose exclusion criteria were very restrictive, women with increased risk factors for VTE (such as obesity, surgery, prolonged immobility) were included in this trial. This is the reason why the incidence of VTE reported is higher than the one referred to in previously available information.

Reminders:

- Every oral contraceptive agent increases the risk of VTE.
- Many factors are associated with an increased risk of VTE, including obesity (BMI > 30), and those should be borne in mind whenever deciding on which contraceptive method to choose.
- Initial data available thus far suggest that the risk of VTE associated with the drospirenone+ethinylestradiol combination may not be significantly different from that associated with other combination contraceptive agents.

Emerging literature and other information from the medicines authorities on this subject should be followed closely.

Isabel Brito Afonso

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