

## From the Editor

*In the previous issues we have focused mostly on data arising from drug safety profile assessments. We have tried to keep up health professionals with issues that are relevant for their daily practice, in an attempt to contribute whenever possible towards our patients' health protection and prevention of iatrogenic events.*

*The pharmacovigilance process, however, depends by its own nature on the active participation of all those who handle medicines, from the lab professional to the prescribing doctor and the patients themselves. In this issue, preliminary safety data resulting from spontaneous ADR reports are presented in respect to two drugs that have lately been under close scrutiny for diverse reasons – nimesulide and sildenafil. Some doubts about their safety profiles may be clarified, whilst others will certainly arise. This will hopefully help to make doctors and pharma-*

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*cists more aware of possible ADRs whose reports may shed more light on current safety concerns.*

## Nimesulide Adverse Reactions Reported to the CNF

Nimesulide is a non-steroid anti-inflammatory (NSAID) sulphonamide whose mechanism of action is characterised by selective inhibition of cyclo-oxygenase 2 (cox2).

This pharmacodynamic profile is compatible with a lower incidence of adverse GI reactions in comparison with other NSAIDs, although this has not been clearly demonstrated.<sup>1</sup> Some studies show that the incidence of this type of ADRs with nimesulide is similar to that of patients treated with a control NSAID. Furthermore, there may appear endoscopically visible lesions of the gastric mucosa with nimesulide<sup>2</sup>, and the selectivity of COX2 inhibition may be lost at higher doses.<sup>3</sup>

The National Pharmacovigilance Centre (CNF) has received, since 1993, 17 ADR reports ascribed to nimesulide. The most frequent ones were skin (5) and liver (4) ADRs. Others were:

peripheral oedema (2), stomatitis (2), paresthesia (1), thrombocytopaenic purpura (1), irritability (1), and headaches/reduced visual acuity (1). No adverse GI reactions have been reported.

The adverse skin reactions reported included three cases of rash, one case of urticaria/angioedema, and one case of necrotising fasciitis which evolved to septicaemia and death. Except for the case of necrotising fasciitis, these ADRs have been previously described with the administration of nimesulide. Several cases of necrotising fasciitis are described in association with various NSAIDs, but this association has never been clearly demonstrated.

Of the hepatic ADRs reported, two cases were compatible with Reye's syndrome. They occurred in children and were both fatal. One case of cholestasis, and another of liver enzyme

elevation and coagulopathy were also reported, the latter being fatal. Liver enzyme elevation and acute hepatitis in patients on nimesulide are mentioned in the literature.<sup>4,5</sup> In the cases reported to the CNF, all patients were concomitantly medicated with amoxicillin+clavulanate. Similarly, one of the patients who died of Reye's syndrome had also been given lisine salicylate.

Although the reporting professionals ascribed a causal relationship to nimesulide, one cannot firmly exclude the direct role of the amoxicillin+clavulanate association in causing liver damage, whose occurrence has been described with the use of this antibiotic (see Vol.1, n.º 4). On the other hand, it is not known whether there may be an interaction between nimesulide and amoxicillin+clavulanate which may potentiate the hepatic dysfunction induced by any one of these drugs.

Reporting to the CNF all serious ADRs that may be related to the use of nimesulide given alone or in combination with other

drugs, is of the utmost importance to make these safety issues clearer. 98.Oct.12

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- <sup>1</sup> Davis R, Brogden RN. Nimesulide. An update of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1994; 48(3):431-54.
- <sup>2</sup> Porto A, Almeida H, Cunha MJ, Macciocchi A. Double-blind study evaluating by endoscopy the tolerability of nimesulide and diclofenac on the gastric mucosa in osteoarthritic patients. *Eur J Rheumatol Inflamm* 1994; 14 (4): 33-8.
- <sup>3</sup> Wallace JL, Bak A, McKnight W, Asfaha S, Sharkey KA, MacNaughton WK. Cyclooxygenase 1 contributes to inflammatory responses in rats and mice: implications for gastrointestinal toxicity. *Gastroenterology* 1998; 115 (1):101-9.
- <sup>4</sup> Selig J, Liberek C, Kondo Oestreicher M, Desmeules J, Stoller R, Dayer P. Nimesulid hepatotoxicity. Sixth Annual Meeting - European Society of Pharmacovigilance. Budapest, September 28-29, 1998.
- <sup>5</sup> Van Steenberghe W, Peeters P, De Bondt J, Staessen D, Buscher H, Laporta T, et al. Nimesulide-induced acute hepatitis: evidence from six cases. *J Hepatol* 1998; 29 (1): 135-41.

TRADE MARK NAMES OF NIMESULIDE WITH MARKETING AUTHORISATION IN PORTUGAL:  
Aulin®; Donulide®; Jabasulide®; Nimed®; Sulimed®

## Tramadol and Risk of Addiction and Respiratory Depression: Changes in the SPC

Tramadol is a central opioid, codeine-analogue analgesic, which may be given through the oral, rectal, intramuscular or intravenous routes, for the treatment of acute, moderate to severe pain. It is a  $\mu$  and  $\kappa$  receptor agonist, and is capable of inhibiting noradrenaline re-uptake and of stimulating serotonin release, thus modulating central pain perception and providing a broader anti-nociceptive effect.

Tramadol is, for its most part, metabolised by the liver (under the control of the polymorph CYP3A4 isoenzyme of cytochrome P450), originating an active metabolite (M1) with opioid-like activity. Tramadol is predominantly eliminated through the kidneys, and its active metabolite has an elimination half-life of 6 to 9 hours.

Initially viewed as a central analgesic drug with a lower risk for addiction and cardiac and respiratory depression, these safety profile aspects have recently been reassessed. Tramadol's Summaries of Product Characteristics (SPC) have been subjected to some changes, in order to make them more uniform and to underscore the above aspects.

The chapter on SPECIAL PRECAUTIONS OF USE will now read as follows:

- *Tramadol shows a low potential for causing addiction. Its prolonged use may be associated with tolerance and physical and psychological addiction. In patients prone to drug abuse and addiction, treatment with tramadol should be restricted to short courses, and must take place under strict medical supervision.*
- *Tramadol must be used with caution in opioid-sensitive patients.*
- *As a pain-killer, tramadol must be used with caution in opioid-dependent patients, in patients with head*

*trauma, shock, reduced levels of consciousness of uncertain origin, respiratory centre or function disturbances, or increased intracranial pressure.*

- *Tramadol is not adequate for the treatment of opioid withdrawal syndrome. Although it is an opioid agonist, tramadol does not suppress morphine withdrawal symptoms.*
- *Seizures have been reported in patients treated with tramadol in the recommended doses. This risk may be increased when the dose of tramadol exceeds the maximum daily dose (400 mg). Tramadol may increase the risk of seizures in patients treated with other drugs that lower the seizure threshold. Epileptic or seizure-prone patients should only be treated with tramadol after its risk-benefit ratio has been duly pondered.*

As for UNDESIRABLE EFFECTS, the following aspects should be noted (among others already highlighted in previous versions of the SPC):

- *Nausea and vertigo were reported frequently (> 10%).*
- *Vomiting, constipation, sweating, dry mouth, headaches, and visual disturbances, may occasionally (1-10%) occur.*
- *Addiction may occur. Withdrawal symptoms similar to those characteristic of opioid withdrawal may occur, namely: agitation, anxiety, irritability, insomnia, restlessness, tremor, and GI symptoms.* 98.Jul.31

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TRADE MARK NAMES OF TRAMADOL WITH MARKETING AUTHORISATION IN PORTUGAL:  
Euflore®; Paxilfar®; Theradol®; Tramadol caps®; Tramal®; Travex®.

# Sildenafil: Reported ADRs and Safety Profile

Sildenafil was approved by the FDA in 98-03-27 for the treatment of erectile dysfunction, based on clinical trials that included over 3,700 patients. This drug received favourable appreciation by the EMEA's CPMP on the 27th of May 1998, and was approved by the European Committee on the 14th of September 1998 as a prescription-only medicine.

- Safety data from clinical trials

Sildenafil's safety profile was assessed in a series of double-blind, placebo-controlled clinical trials, with a total of 2,722 patients medicated for 6 months, as well as in 10 open-label studies with 2,199 patients treated during one year. The most frequently identified adverse reactions in the pre-marketing phase were: headaches (16%), flushing (10%), and dyspepsia (7%). Other reactions described included nasal congestion, visual disturbances, and diarrhoea.

The adverse effects identified were, in general, mild or moderate, and of short duration. Discontinuation of therapy due to adverse reactions occurred in about 2% of treated patients.

- Data from ADRs spontaneously reported to the FDA

From the time the drug was marketed in the USA (March, 1998) to the end of June, more than 2.7 million prescriptions of sildenafil were dispensed. During this period, 123 cases of patients that died supposedly after taking sildenafil were reported to the FDA. In 30 of these patients (24%), report reliability was questionable, in that the source was not identifiable, information had been passed on to third parties who had heard of those cases, or who had known about them through non-medical press. Additionally, in 12 patients, the reporting person said that the use of sildenafil had not been confirmed.

The FDA analysed in further detail the reports pertaining to the 69 patients who were proven to have died after taking sildenafil. Their average age was 64 years (29-87 years). In 21 patients, the cause of death was not mentioned, or was unknown. Of the remainder, two had a stroke, and 46 had cardiac events. In 12 patients, nitroglycerine or other nitrate-containing medication had been administered. This association with sildenafil is contraindicated. In 51 of the 69 patients, one or more coronary risk factors were identified (high blood pressure, hypercholesterolaemia, smoking, diabetes, obesity, or past cardiac events).

- Data from spontaneous reports to the holder of marketing authorisation (Pfizer)

The first safety report, corresponding to the period from the 27th of March (FDA approval) to the 15th of June, was made available to the EMEA and to the member-states in the beginning of July. During that period, Pfizer received 125 spontaneous

reports of serious ADRs and 171 reports of non-serious events associated with the use of sildenafil. The non-serious events were mostly reduced (46 cases) or no (27 cases) therapeutic response, and impotence (18 cases). Other frequently reported secondary effects were headaches, visual disturbances, and flushing.

Of the 125 serious cases reported, 115 were deemed unexpected according to the SPC approved in the USA. These cases included 35 fatal outcomes, in 17 of which the cause of death was not known. In the remainder, the cause of death was stroke (2) or cardiac events.

The non-fatal cases included cardiac manifestations (from myocardial infarct to cardiac arrest and pulmonary oedema), stroke, disturbances of cardiac rhythm, hypotension, priapism or prolonged erection, and visual disturbances (blurring, vitreous haemorrhage, or loss of vision).

- Conclusions

The analysis of the safety data emerging from clinical trials and spontaneous ADR reports in patients medicated with sildenafil allows one to draw the following conclusions:

- There does not seem to be a higher frequency of adverse reactions in the post-marketing phase, when compared with the research phase.
- As for unexpected adverse events, and especially in what concerns fatal outcomes, many such occurrences could be considered to be expected, independently of sildenafil, given the age of the patients and the diseases from which they suffered (heart disease, diabetes, high blood pressure).
- Virtually all reported deaths occurred in patients with a contraindication to sildenafil, namely high coronary risk and/or nitrate therapy. These contraindications and precautions are, in any case, included in the approved SPC.
- Within this context, the currently available data pertaining to sildenafil and emerging from spontaneous ADR reports do not alter the currently known safety profile of this drug.  
*98.Oct.12*

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TRADE MARK NAMES OF SILDENAFIL WITH MARKETING AUTHORISATION IN PORTUGAL:  
Patrex®; Viagra®.

*If you suspect that your patient might have symptoms and/or signs of an adverse drug reaction, and especially if the event is unexpected, incapacitating or severe - REPORT IT!*

# Cisapride and Arrhythmia Changes in the SPC

Cisapride is a gastrointestinal prokinetic drug that has been under review by the CNF in what concerns its safety of use in children and its potential to induce cardiac arrhythmia (see Vol. 1, N.º 4).

Recent experimental evidence suggests that cisapride in therapeutic concentrations has direct electrophysiologic effects on the ion flows responsible for cardiac depolarisation. This may explain the rare cases of ventricular arrhythmia and QT-interval prolongation reported internationally. In most cases, the patients also had other risk factors for arrhythmia, or were simultaneously medicated with drugs which inhibit cytochrome P450 or prolong the QT interval themselves.

The CNF has deemed it necessary to change the SPC of all medicines whose active substance is cisapride. Among others, the following data have been included in their corresponding chapters:

## • CONTRAINDICATIONS

- *Simultaneous oral or parenteral administration of potent CYP3A4 inhibitors such as: oral antifungal agents; macrolide antibiotics such as erythromycin, clarithromycin, or troleandomycin; HIV protease inhibitors; nefazodone.*
- *Premature new-borns (less than 36 weeks' gestation) from birth to three months of age.*

## • WARNINGS AND SPECIAL PRECAUTIONS OF USE

*It is advisable to avoid the use of cisapride in patients with the following risk factors for cardiac arrhythmia:*

- *Non-corrected water and electrolyte imbalances (potassium/magnesium), such as those occurring in patients who take potassium-depleting diuretics, or insulin in acute settings.*

- *Renal failure (especially patients on chronic dialysis).*
- *Significant obstructive airways disease.*
- *Respiratory failure.*
- *Conditions associated with QT-interval prolongation (such as congenital prolonged QT syndrome, prolonged QT interval associated with diabetes mellitus, association with drugs known to cause QT-interval prolongation).*
- *History of known heart disease (including severe ventricular arrhythmia, 2nd or 3rd degree AV block, congestive heart failure, ischaemic heart disease).*

In patients who have or are suspected to have the above-mentioned risk factors, the risk-benefit ratio should be carefully pondered before starting therapy with cisapride.  
98.Oct.08

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TRADE MARK NAMES OF CISAPRIDE WITH MARKETING AUTHORISATION IN PORTUGAL:  
Aceleran®; Cismotil®; Clotioride®; Coordinax®; Dispepci®; Prepulsid®.

All ADR reports get fully grounded, individualised, and strictly confidential feedback from the National Pharmacovigilance Centre.

## Drugs under assessment\*

• albumin • amoxicillin + clavulanate • anti-histamines (non-sedative) • appetite suppressants • aprotinine • association of caffeine with salicylates, pyrazolone, paracetamol • bromocriptine • camphor • carvedilol • cisapride • clozapine • contrast media (high osmolarity) • corticosteroids (inhaled) • dipyridamole • droperidol • glimepiride • glipizide • halogenated anaesthetics • hormonal replacement therapy • isotretinoin • ketorolac • meloxicam • methadone • montelukast • nicotine • nimesulide • nucleosides (analogues) • oral contraceptives • pancreatine • phenilpropalamine + pseudo-ephedrine • piroxicam • protease inhibitors • selective serotonin re-uptake inhibitors (SSRIs) • sertindole • sildenafil • tamoxifen • ticlopidine • tramadol • vigabatrim • zafirlukast

\* The drugs in this issue are in bold-faced type. This is a list of the medicines currently under special assessment (monitoring/information) at the National Pharmacovigilance Centre. These drugs, however, do not necessarily correspond to products with problems that may imply some change in their SPCs or marketing authorisations.