boletim de FARMACOVIGILÂNCIA

Ministério da Saúde

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

VOLUME 12
NÚMERO 4
4TH QUARTER 2008

Editor's Notes

The Director has the floor:

The INFARMED Medicines Risk Management Dept is now nearing the end of a restructuring process. Two operational working groups have been created under the aegis of the National Pharmacovigilance System Management Unit: ***Signal Detection*** *and* ***Risk Management****.*

In the shorter run the National Pharmacovigilance System will need to be strengthened by means of an expected increase in reporting rates and programmes aiming for risk minimisation for certain medicines. This is a demanding challenge that affects all involved parties in cross-sectional fashion.

We have therefore set up a periodical and demanding ***Training and Information*** *programme for the next three years. Two* ***Information Mornings*** *and the* ***First National Risk Management and Pharmacovigilance Meeting*** *have already taken place. In these events the following themes were discussed: Risk Management Plans, National Pharmacovigilance System, Electronic Transmission of ADRs, and Periodic Safety Update Reports, among others. In 2009, thanks to a broad basis of collaboration from all health professionals, our goals will naturally be expanded.*

Greater safety, better public health is our motto.

Júlio Carvalhal

Ibuprofen and Acetylsalicylic acid: Risk of Interaction

Acetylsalicylic acid (ASA) in small doses has a cardiovascular protective effect due to irreversible inhibition of the cyclo-oxygenase-1 enzyme (COX-1), which compromises platelet aggregation. Non-selective non-steroidal anti-inflammatory agents also inhibit COX-1, but they do it by reversibly linking to the isoenzyme's active core. However, most active ingredients from this pharmacotherapeutic group do not completely inhibit this isoenzyme when given in doses within therapeutic range. It follows that competitive interaction between ASA and non-selective NSAIDs will decrease the cardioprotective effects of ASA when both medicines are given simultaneously.

Within the scope of an analysis conducted by the European Pharmacovigilance Working Party (PhVWP), it was seen that an interaction had been observed in several pharmacodynamics studies when ibuprofen 400 mg (either in one single dose or divided into multiple doses) was administered simultaneously with ASA. This effect was not seen with other NSAIDs (diclofenac, paracetamol, rofecoxib). In experimental studies, giving a single dose of ibuprofen 400 mg **simultaneously within 8 hours before or 30 minutes after administration of immediate release ASA** caused a clinically significant reduction of ASA's effect on thromboxane production and therefore on platelet aggregation.

Although the **clinical implications** of this interaction are **not fully understood**, it is of potential clinical relevance, given that ASA's cardioprotective effect may be blunted namely when used for secondary prevention of myocardial infarction and stroke.

Consequently, the PhVWP has deemed it necessary that information on the risk of interaction be included in the SPCs and Information Leaflets of medicines containing either ibuprofen or ASA. This was put into practice by the Risk Management Dept in October last: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/ALTER_TIPO2_SEGURANCA (in Portuguese only).

Margarida Guimarães

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
PIL	Patient 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

Medicines Risk Management Dept. (Pharmacovigilance) at INFARMED I.P.
Ph.: 217 987 140 - Fax: 211117541
E-mail: farmacovigilancia@infarmed.pt

OR

Northern Regional Pharmacovigilance Unit
Tel: 225 513 661 - Fax: 225 513 682
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

Risk of Atrial Fibrillation associated with Pamidronic Acid

Following a PhVWP assessment, it has been concluded that the risk of atrial fibrillation associated with the use of biphosphonates seems to be low, and the attending **risk/benefit ratio stays favourable**. Section 4.8. *Undesirable Effects* of the SPC of this medicine will now read:

> When the effects of zoledronate (4 mg) and pamidronate (90 mg) were compared in a clinical trial, the number of cases of adverse reactions consisting of atrial fibrillation was higher in the pamidronate group (12/556, 2.2%) than in the zoledronate group (3/563, 0.5%). In another clinical trial including patients with postmenopausal osteoporosis, it had been previously observed that patients treated with zoledronate (4 mg) had had an increased rate of serious ADR cases of atrial fibrillation when compared to placebo (1.3% compared to 0.6%). The mechanism underlying the increased incidence of atrial fibrillation with therapy with zoledronate and pamidronate is unknown.

Margarida Guimarães

INDEX CARD | **Director:** Júlio Carvalhal **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Ana Araújo, Cristina Rocha, Fátima Bragança, João Ribeiro Silva, Madalena Arriegas, Paula Roque, Pedro Marques Silva. **Publishing Assistant:** Adélia Noronha. **Advisory Board:** Vasco Maria, Luísa Carvalho, Hélder Mota Filipe (INFARMED, I.P. Executive Board); INFARMED, I.P. Medicines Evaluation Committee. **Publisher:** INFARMED - National Authority of Medicines and Health Produts, I.P., Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, E-mail: 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

ADRs in a Neonatology Unit

Medicines efficacy and safety data concerning paediatric populations are generally scarce, since regulatory authorities and the pharmaceutical industry do not routinely evaluate this type of parameters in these patients. However, off-label use of medicines in children is common practice and this could lead to a higher toxicity risk. Additionally, the pharmacological activity of medicines is different in children than in adults, which may cause diverse adverse event patterns and make this age group – especially newborns – a highly vulnerable one. The **incidence of ADRs** in paediatric hospitals is higher than that found in general and community hospitals, and is very high in **neonatal care units**, where it can reach up to **10 to 30 percent**.

Objectives:

To study the frequency and characteristics of adverse drug reactions in the paediatric population admitted to the Santa Maria Hospital Paediatric Department Neonatology Unit (NU).

Overview of methods:

This study had an observational component as well as an analytical component of the case-control type. The sample included all newborns admitted to the NU in the months of April, May and June 2004. An analysis was conducted comparing the group of patients who sustained ADRs and the group of patients who did not. The study's protocol was submitted to and approved by the hospital's Ethics Committee.

The Results in Brief:

The samples included 32 (37.2%) female patients, their mean age at date of admittance was 8.2 days, mean gestational age was 33.0 weeks, mean Apgar index at 1 and 5 minutes was 7.6 and 9.2 respectively, mean weight at birth 2,014.4 g, mean duration of hospitalisation episode 15.3 days, and mean number of medicines given before admittance was 3.5. During the observation period there were no admissions due to ADRs.

The incidence of ADR episodes per 100 patient.days of hospitalisation was 1.7 ($CI_{99\%}$ 0.8-2.6), and the incidence of ADR episodes per 100 patient.days of exposure to medicines was 1.7 ($CI_{99\%}$ 0.8- 2-7). The incidence of **patients with ADRs per 100 patient.days of hospitalisation was 1.4** ($CI_{99\%}$ 0.5-2.2), and the incidence of patients with ADRs per 100 patient.days of exposure to medicines was 1.4 ($CI_{99\%}$ 0.6-2.3). Twenty-two ADRs were detected in 18 patients (8 ♂) with a mean **1.2 ADR per patient**.

Regarding the 22 ADRs diagnosed, most (59.1%) were laboratory parameter changes, namely increased serum levels of **urea and creatinine**, whose MedDRA classification corresponds to the *Investigations* class. Other classes involved were *Respiratory, thoracic and mediastinal conditions* (13.6%), *Metabolism and nutrition conditions* (9.1%), and *General conditions and conditions relative to site of administration* (9.1%).

The pharmacological class most frequently associated with the ADRs observed was **aminoglycosides (half of all cases)**. Individually, gentamycin was suspected to have caused 27.3% of cases, netilmycin 13.6%, while 2 cases (9.1%) were ascribed to both drugs given sequentially. The other medicines were poractant alpha with 2 cases; hydrochlorthiazide; heparin; saline and electrolyte solutions; dopamine; vancomycin; normal human immunoglobulin; phentanyl; ranitidine, ampicillin and netilmycin administered concomitantly; and glucose 10% solution – all these with a relative frequency of 4.5%.

As for seriousness, **27.3% of the ADRs were classified as serious**. Out of these, **9.1% put the patient's life at risk** and 18.2% were considered to be clinically relevant. No death was ascribed to an ADR. Serious ADRs consisted of one case of aggravated oedema with saline/electrolyte solutions, one case of dopamine-associated elevated arterial blood pressure, one case of respiratory failure attributed to phentanyl, two cases of pneumothorax with poractant alpha, and one case of elevated blood serum levels of urea, creatinine and potassium associated with gentamycin.

Of all the non-serious ADRs, the majority (11 out of 16) consisted of increased blood serum levels of urea and creatinine ascribed to the use of aminoglycosides. The remainder were isolated cases of thrombocytopoenia ascribed to heparin, decreased blood serum levels of sodium ascribed to hydrochlorthiazide, hyperglycaemia ascribed to human immunoglobulin, erythematous macula ascribed to netilmycin, ranitidine and ampicillin given concomitantly, and generalised oedema ascribed to 10% glucose solution.

Using the WHO probability grades, **31.8%** of the detected ADRs were classified as **probable**, 31.8% as possible, 31.8% as improbable. One case (4.5%) was unclassifiable in that complete data were lacking. Of all the ADRs, **86.4% were expected**, whereas 13.6% were of the unexpected type. Regarding their pharmacological classification, **77.3%** were **type A** ADRs, 13.6% type B, and 9.1% type F.

A total of 63.6% of ADRs called for changes in the therapeutic regime and 18.2% required specific medical treatment. The ADRs observed took on average **1.3 days to show overt manifestations**, and their **mean duration** was **6.6 days**. Serious ADRs took shorter to manifest and longer to resolve than non-serious ADRs.

The **patients who sustained ADRs**, in relation to those who did not sustain any, showed:

- **lower age** at date of admittance (0.6 *vs.* 10.7 days), *OR*=6,4 ($CI_{99\%}$ 0.9-143.6)
- **lower gestational age** (29.7 *vs.* 33.6 weeks), *OR*=19,9 ($CI_{99\%}$ 1.9-4.7)
- **lower birth weight** (1,454.1 *vs.* 2,129.7 g), *OR*=10.7 ($CI_{99\%}$ 1.5-237.7)
- **longer duration of hospitalisation episode** (29.7 *vs.* 12.1 days), and **higher number of medicines administered** during hospitalisation (19.1 *vs.* 8.7), longer duration of exposure to medicines during hospitalisation (29.4 *vs.* 11.6 days), and higher number of adverse events detected during hospitalisation (5.6 vs. 2.0).

Patients sustaining ADRs presented an **associated respiratory condition in 94.4% of cases**, whereas of those who had no ADRs only 55.6% had such an associated condition; *OR*=13.6 ($CI_{99\%}$ 1.3-2.974.5).

Discussion and Conclusions:

The 22 cases of ADRs detected generated an incidence of ADR episodes of 22/1,312.5 children.days of hospitalisation, which corresponds to **22/1,261 children.days of exposure to medicines**. When incidence is given as number of **patients with ADRs** per total number of patients admitted, a figure of **20.9%** is obtained, which is very similar to other published studies.

The rate of hospital admissions due to ADRs could not be calculated, since there were no patients during the observation period who had an ADR as a reason for admittance. According to other authors, **ADR associated admission rates** in neonatology units are usually low – approximately 0.2% of the total of admissions. One of the possible explanations for this is the fact that newborns who are not hospitalised are not in principle exposed to a high number of medicines, apart from the usual vitamin supplements and vaccines, which decreases their risk of sustaining an ADR. On the other hand, these newborn babies should not have any renal or liver function impairments, which could otherwise facilitate the occurrence of ADRs.

When one compares our results concerning the type of **drugs involved** with the existing literature data, it becomes clear that they **overlap**; antibacterial agents (aminoglycosides and others), diuretics (thiazidic and other), heparins, and saline/electrolyte solutions predominate. In our study however, other medicines equally mentioned in the literature were not found, namely glucocorticoids, local anaesthetics and anticonvulsants. This may be due to differences in prescribing patterns and in the types of conditions affecting newborn populations. The type of drugs associated with ADRs corresponds to the type of drugs prescribed

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)

to the greater number of the NU patients. Nevertheless, there were some classes of drugs prescribed to a high number of patients which were not associated with ADRs (xanthines, parentheral feeding products, blood products, penicillins, cephalosporins, topical antibiotics and antifungals, laxatives, and vitamins). This could be explained by their relatively broad safety margin, or alternatively by insufficiently sensitive ADR detection methods.

Regarding the **proportion of serious ADRs**, the values described by other authors are within the **20%** range, which is in agreement with our results. The fact that most ADRs detected in this study were expected and type A leads us to think that, at least theoretically, there might be some room for preventive intervention, either by developing and implementing clinical guidelines or protocols, or by improving the monitoring of patients exposed to higher risk drugs. However, it should be underscored that it is already common practice in this NU to periodically monitor the renal function in patients exposed to aminoglycosides. The rate of ADRs requiring changes in therapy or specific medical treatment in this study is in accordance with the figures presented by other authors.

From the comparative analysis of the group of patients with ADRs versus the group of patients who sustained no ADRs, it should be highlighted that the patients who suffered ADRs during their hospitalisation episode were younger on admittance date, more premature, lighter at birth, and had an associated respiratory condition. The results from this study also agree with the findings by other authors pointing to the following **risk factors for the occurrence of ADRs in newborns**: low gestational age, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, ventilatory therapy, parentheral feeding, raised liver transaminases, apnoea, and renal failure.

We conclude that ADRs are not a frequent reason for admittance at the study hospital's neonatology unit. However, there was a **high incidence of ADRs** during the hospitalisation episodes. This highlights the relevance of this matter in the hospital setting and especially in units where highly specialised and complex care is provided to patients with critical conditions. Bearing this is mind, though most ADRs detected were not serious and rarely put the patients' lives at risk, their occurrence generates further needs for care provision with all their attending costs and other consequences.

It would be interesting to conduct further studies to determine other types of factors associated with the occurrence of ADRs in children. Concerning paediatric patients various obstacles exist that hinder the promotion of the rational use of medicines, namely the scarcity of available data regarding the risk of occurrence of ADRs, as well as the complexity of appropriate dosing and of adequacy of prescription in the absence of effectiveness studies. These hurdles may be overcome by conducting clinical trials in paediatric populations as well as observational post-marketing surveillance studies, in such a way that effective ADR prevention strategies may be devised in the future.

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Ana Marta Anes (Lisbon and Tagus Valley Regional Pharmacovigilance Unit)

Acomplia® (Rimonabant) suspended

Acomplia® (rimonabant) was approved in the European Union in June 2006 as an adjuvant to diet and exercise in the treatment of obese or overweight patients with associated risk factors. Although it was authorised in all member states, this medicine was never marketed in Portugal.

The CHMP has come to the conclusion that the risk of psychiatric disorders in obese or overweight patients treated with Acomplia® is approximately twice that of placebo. It has also been observed that the efficacy of this medicine in clinical practice is more limited than what had previously been thought based on clinical trials. It was therefore concluded that the benefits of Acomplia® were no longer considered to be higher than its risks and it was recommended that its marketing authorisation be suspended in the EU.

Medicines and Medical Devices for Preventing and Treating Human Pediculosis

Pediculocide products containing any of the active ingredients in the box are considered to be medicinal products.

- Benzyl benzoate
- Crotamiton
- Dimethicone
- D-fentizide
- Nalathiol
- Permethrine
- Piperonyl
- Quassia amara

Pediculocide products whose secondary storage contains a medical device or a cosmetic or bodily hygiene product associated with the medicine are also considered to be medicinal products. On the other hand, there are some products in the market which are classified as medical devices on account of their principal mode of action in preventing and treating human lice infestation. In this case the mechanism underlying the wanted effect is of a physical/mechanical nature – this group includes specific anti-lice **combs**.

Other adjuvants for the treatment of human pediculosis can also be found in the market, such as bodily hygiene products consisting of **shampoos** to be used after the therapeutic agent is applied. However, these products may not contain in their active ingredients any of the pediculocide substances included in the list above.

ADRs in the Literature… **Acute Psychosis? Think medicines!...**

The authors report the occurrence of acute psychosis after giving amoxicillin+clavulanic acid for suspected pneumonia to a 55-year old woman. A strong temporal relationship and recurrence after drug rechallenge were observed. Symptoms coincided with the expected peak circulating drug concentrations at about one hour. We are reminded to consider the possibility of drug induced acute psychosis, even in the absence of pre-existing psychiatric illness or other predisposing factors.

Bell CL, Watson B, Waring WS.
BMJ 2008;337:a2117

Anaphylactic Shock to Patent Blue V
An Example of Safety Signal Generation

Patent Blue V (also known as Sulphan Blue or Food Blue 5) is a diagnostic medicinal product used for dying lymph vessels for lymphangiography and arterial area mapping. Its use has been increasing for the **detection of sentinel nodes in breast cancer**. In Portugal its use is limited to hospital units and subjected to **special authorisation**. This type of special authorisation might make one think that this is a relatively little used product. However, in 2005, authorisation was given to 2,285 2-ml vials of 2.5% Patent Blue V, in 2006 this **grew** to 33% (3,035 vials), and in 2007 up to 62% (3,690 vials). In terms of geographical distribution, 4,800 vials were ordered in the Northern region of the country, 2,900 in the Lisbon and Tagus Valley region, 800 in Central Portugal, and the remainder in the Southern region and the Azores islands. Recommended dosage is 1 to 10 ml (1/2 to 5 vials) and the **route of administration is subcutaneous or intravascular**.

Following an increase in the use of this technique of sentinel node mapping, an increased incidence of anaphylaxis to Patent Blue V would be expected. Since there is not an MA Holder for this product in this country, putting safety measures into action entails some difficulty. As a consequence, both the users (hospitals) and the National Authority (INFARMED I.P.) are left with incremented responsibility.

Anaphylactic shock with Patent Blue V, according to the French SPC, was expected to be a very rare adverse reaction, and was not described in the Information Leaflet. This is mentioned because special authorisation for the use of this medicinal product in Portugal is given based on the original French marketing authorisation. The National Pharmacovigilance System had entered three cases until October 2007, one of which had been a case of pre-shock and the other two of full-blown anaphylactic shock.

The **first case** was reported in 2005 by a general surgeon regarding a 16-year old patient submitted to a node biopsy procedure and who presented with a **"blue" rash**, hypotension and tachycardia, without bronchospasm – pre-shock caused by anaphylaxis to Patent Blue V. She was treated with methylprednisolone, adrenalin and ventilation for about 12 hours. The ADR occurred **20 to 30 minutes after administration** of Patent Blue V, and evolved to complete recovery in approximately 12 hours.

A **second case** was reported in 2006 concerning a 52-year old patient submitted to a breast cancer sentinel node detection procedure who sustained anaphylactic shock for one hour with oedema, rash and bluish discoloration of face, neck and trunk. The ADR appeared **30 minutes after administration** of Patent Blue V and resolved completely. The **bluish discoloration** was so intense that the physician felt it necessary to express his surprise in the report. It persisted 24 hours later and only subsided completely after **48 hours** had elapsed.

The **third case** was reported in 2007 by an anaesthetist. It concerned a 42-year old patient submitted to a sentinel node detection procedure in the setting of a mastectomy. She **suddenly** presented with circulatory collapse: hypotension, tachycardia, hypoxaemia and hypocapnia, without bronchospasm or rash, but showing a **greenish discoloration** of the skin. She was treated with fluids, ephedrine, noradrenalin, hydrocortisone. The ADR occurred **15 minutes after** Patent Blue V had been given and resolved completely. In this case too the reporting physician expressed great concern and surprise.

Taking into account the low rate of ADR reporting in this country, the 3 cases described above were of great relevance in changing the medicinal product's safety profile. The risk of anaphylactic reactions with Patent Blue V was pondered at a European level by weighing reaction seriousness and frequency on the one hand, the usefulness of Patent Blue V for lymph node location and minimisation measures to prevent serious anaphylactic reactions, on the other. It was concluded that the **seriousness and frequency were higher than until then described on the SPC**, and that there currently are no safer alternatives.

Europe-wide, in most cases of anaphylactic reactions, Patent Blue V was administered for the detection of sentinel nodes. In some cases, time elapsed between administration and appearance of the anaphylactic reaction was less than 5 minutes. Most serious cases consisted of anaphylactic shock, evolution was favourable but it was sometimes necessary to give adrenalin until over 12 hours after the reaction had occurred. No fatal cases were reported. A full assessment of the biopsy technique of sentinel nodes in breast cancer and other types of cancer is needed, so that this technique may come to be standardised.

The sensitisation mechanism remains unclear, since almost every patient's reaction occurs on their first known exposure to Patent Blue V. However, previous sensitisation may have occurred due to the broad use of Patent Blue V as a colouring agent (**E131**) in textiles, cosmetics, foods and pharmaceutical excipients, for example.

A proposal was made for the SPC to be altered and for physicians who are potential users of Patent Blue V to be informed, namely radiologists, anaesthetists and surgeons, as well as hospital pharmacists:

Section 4.4 – Warnings and Special Precautions of Use. Following "Before any administration, the patient should be asked about his/her full allergic and/or medicinal intolerance history", it has been added: "**Patent Blue V may cause anaphylactic shock and should only be used in settings where adequate treatment means are available**".

Section 4.8 – Undesirable Effects. The former version read: "Hypersensitivity reactions of the urticarial type and exceptionally angioedema and anaphylactic shock are possible". This has been changed to: "**Immediate hypersensitivity reaction (occurring after a few minutes to some hours); frequent urticaria, infrequent angioedema and anaphylactic shock**" (≥ 1/1000, <1/100).

The safety profile of a medicinal product is ever changing and dependent on experience acquired with its use. Computer-based signal generation methods are currently under development, but health professionals' awareness will always be of great relevance, both for case identification, and for the analysis and research of safety alert signals aiming to protect the public's health.

Reminder: Any serious or unexpected adverse reaction should be reported to the regional Pharmacovigilance Units or directly to INFARMED, I.P.

Major references

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Fátima Pereira de Bragança

Medicinal Plants from A to Z
described adverse reactions

- **Cat's claw** *(Uncaria tomentosa)*
  - Hypotension
  Nº of Medline citations: 11
  Main uses described: anti-inflammatory, contraceptive, antidyspeptic, tonic, immunostimulant, hypotensive.

- **Nettles** *(Urtica dioica)*
  - Hypersensitivity reactions, especially skin (acute contact dermatitis)
  - Oedema, oliguria
  - Dyspepsia
  Nº of Medline citations: 11
  Main uses described: diuretic; arthritis, allergic rhinitis, prostatic hypertrophy.

- **Grape seed** *(Vitis vinifera)*
  - Hypersensitivity reactions
  Nº of Medline citations: 8
  Main uses described: antioxidant, phlebotonic.

- **Juniper** *(Juniperus communis)*
  - Nephrotoxicity
  Nº of Medline citations: 6
  Main uses described: anti-inflammatory.

NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. Their presentation herein is factual and does not mean that therapeutic uses mentioned are approved or implicitly condoned in any way by this publication.
NB 2: 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: "human side effects", "toxicity in humans", "adverse reactions".