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Editor's Notes

A recent survey by the Netsonda Research Group on the usefulness of INFARMED publications concludes that the Boletim is one of the Portuguese Authority's publications that are more well-known across professional groups. It is read by over two-thirds of the physicians and three-quarters of the pharmacists sampled, most of whom consider it to be of interest or of great interest. Over two-thirds of both physicians and pharmacists deem it useful/very useful for their activity with a friendly format, and they are globally satisfied with it as a source of information. However, about 30 percent of physicians stated they were not receiving the Boletim by snail mail. The Boletim's availability online for some time now is in accordance with the trend revealed by the survey to use it in its virtual format.

Whenever the risk-benefit profile of a medicinal product is shown to have become unfavourable, which may only happen several years into its continuing use, the best way to ensure patient safety may include redefining its scope of prescription or, in more extreme cases, even withdrawing it from the market. This may also be the best way to protect public health should a relevant and unexpected quality problem be detected. This issue's articles are good examples of both instances.

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

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www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

National Pharmacovigilance Centre
Tel: 217 987 140 - Fax: 217 987 155
E-mail: farmacovigilancia@infarmed.pt

OR

Northern Regional Pharmacovigilance Unit
Tel: 225 573 990 - Fax: 225 573 971
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

Desmopressin
nasal spray no longer indicated for primary nocturnal enuresis

Desmopressin is a synthetic vasopressin analogue used in the treatment of **central diabetes insipida**, **renal concentration testing**, **primary nocturnal enuresis** (PNU) in children aged 5 years or older, and **nocturia associated with multiple sclerosis**.

Desmopressin shows high antidiuretic activity and a long duration of action when compared to the naturally occurring peptide. The **nasal** formulation has **greater bioavailability** than the oral one. Both oral and nasal formulations cause prolonged urinary retention and decreased osmolarity, which may result in hyponatraemia and water intoxication. It is not known whether these untoward effects are dose-related, but there is strong evidence for an association with the nasal formulation. ADR reporting rates for hyponatraemia, for instance, are approximately 3 to 4-fold higher for the nasal spray than for the oral tablets.

It has been concluded from the assessment carried out by the European Pharmacovigilance Working Party that the **risk-benefit profile** of desmopressin nasal spray is **negative** when used for **PNU in children 5 years or older**. When compared to other formulations of desmopressin, the nasal spray accounted for most serious ADRs reported in patients with PNU. Those reactions were more frequently reported in **children** than in adults, and included **hyponatraemia, water intoxication and seizures**.

Madalena Arriegas

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

INDEX CARD | **Director:** Regina Carmona **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Alexandra Pêgo, Ana Araújo, Catarina Martins, Eugénio Teófilo, Fátima Bragança, João Ribeiro Silva, Madalena Arriegas, Paula Roque, Pedro Marques da Silva, Regina Carmona, Susana Gonçalves, **Advisory Board:** Vasco Maria, Luísa Carvalho, Helder Mota Filipe (INFARMED Executive Board); INFARMED Medicines Evaluation Committee. **Publisher:** INFARMED-Instituto Nacional da Farmácia e do Medicamento, Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, correio elertrónico: 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

Incidence and nature of Medication Errors in Neonatal Intensive Care Un safety-enhancing strategies

A literature review (PubMed e EMBASE) was published in Drug Safety on the incidence and nature of medication errors in neonatal intensive care units (NICUs), and strategies to improve safety.

Newborns are highly vulnerable to medication errors owing to their exposure to medicinal agents in neonatal intensive care units, the relative lack of scientific rationale for many pharmacological interventions on them, and the lack of formulations specifically developed for this age group. Most published studies on medication errors have been conducted on adults and older paediatric populations, and extrapolation to this age group is not straightforward. Epidemiological data on medication errors in newborns and neonatal intensive care units is therefore scarce.

When compared to other population groups, newborns pose special challenges to the health system regarding prescribing, dispensing, administering and monitoring of medicines. Above all, **there are no studies** showing the efficacy and safety of a large number of medicinal products used in this population. Prescribing decisions involving newborn babies have to be made on a case by case basis, due to both interindividual and intraindividual heterogeneity, the former associated namely with differing gestational ages at birth, and the latter with factors such as weight, length, enzymatic system maturation, and renal function variations. These factors affect the ability to tolerate medicines and call for frequent fine tuning of dose and drug administration intervals.

Any medicines used in NICUs are either authorised and being used off-label, or not authorised and being used under a special authorisation clause. In the UK, for instance, 45 to 60% of medicines in NICUs on average are used for off-label indications, and in 10 to 16% they are not authorised.

The lack of standard references for medicine dosage when in off-label or otherwise *unauthorised* use explains why practitioners often have to deal with **diverging guidelines for the same medicinal products**. As a result of the limited number of medicines that are available in dosages appropriate to this age group, and of the almost universal need to prescribe according to weight, more calculations and dilutions and necessary than for adults, which generates an increased number of opportunities for error.

Types of medication errors described

Although some authors describe administration errors as being the most frequent ones, the **more frequently** detected medication errors were **dosing errors**. These occur due to incorrect or outdated records of the patients' weight, incorrect recording of the therapeutic regime, incorrect measurement units (e.g., milligrams substituted for micrograms or vice-versa), and incorrect placement of the decimal point when calculating the dose. The errors that were potentially more serious included overdoses of 10 to 100–fold.

Some authors report errors more frequently **on prescribing** than when preparing or administering medicines, whereas others describe just the opposite, especially dilution errors for adult formulations.

Other types of errors found include: errors in administration route, errors in parentheral nutrition, switching patient identification, and prescribing discrepancies.

Strategies to improve safety

✓ ***Computerised prescription and other technological tools***

Few studies have looked on the impact computer-based prescription and other technological aides (e.g., bar codes ascribed to medicines and patients, use of computerised intravenous devices, specific software for instant, real-time updating of patient's weight) may have in reducing medication errors in this specific population. **Most studies** suggest there could be a **major decrease** (66-94%, with an associated clinical decision supporting system) **in prescription-related medication errors** after rolling out a computer-based prescription system. **However**, in one study increased mortality was observed in a paediatric hospital immediately after computer prescription was set up, which was thought to result from delays in administration of urgent medication, increased time spent by physicians away from the wards while carrying out computer-related activities, or from the inevitable period of adaptation *per se*.

nits:

✓ ***Intervention of clinical pharmacists***

The few existing studies have used varying ing methods to assess the impact pharmaceutical intervention may have in reducing medication errors. In general, **pharmacokinetic monitoring** and **clinical prescription review** (dose, incompatibilities, interactions, route of administration) by pharmacists were considered to be relevant and of added value, namely regarding allergies, probability of ADRs, lab test results, possible effects of medicines taken by mothers during pregnancy and delivery. Other activities viewed as important such as participation in the organisation (in multidisciplinary procedure development teams, and in designing drug prescribing and administration guidelines) and training activities were not evaluated in the above-mentioned studies. Pharmacists may give a special contribution with information on product dilution and reconstitution, compatibility of intravenous mixtures and perfusion velocities, and in the field of parentheral nutrition.

Susana Gonçalves

* Chedoe I, Molendijk H, Dittrich S, Jansman F, Harting J, Browers J, Táxis K. Incidence and nature of medication errors in neonatal intensive care with strategies to improve Safety – a review of the current literature. Drug Safety 2007: 30 (6): 503-513.

Veralipride
Europe-wide withdrawal

Veralipride is a neuroleptic approved since 1979 for the treatment of menopause-associated vasomotor symptoms. Following an assessment of all available data on its safety and efficacy, EMEA concluded that the risk-benefit ratio of veralipride (Agreal®) is unfavourable; apart from its limited efficacy, veralipride is associated with significant secondary effects, including **depression, anxiety, and tardive diskynesia** (a movement disorder that may be protracted or even irreversible), which may occur during or after treatment. Therefore, this medicine **will no longer be available for prescription and dispensing from September 2007**.

Recommendations for healthcare professionals:

- Women undergoing therapy with veralipride should be urged to see their doctor in order to discuss other treatment options.
- Prescribers should not write any new prescriptions for veralipride. Their patients currently on veralipride should have it discontinued or switched to another drug.
- Since abrupt withdrawal of veralipride may cause symptoms such as anxiety, insomnia and depression, the dose of veralipride should be gradually reduced over a period of one to two weeks.

Madalena Arriegas

Piroxicam
restrictions to prescription

EMEA has recommended that the use of piroxicam be restricted on account of an associated **higher risk of serious GI and skin ADRs** than for other non-selective, non-steroidal anti-inflammatory drugs (NSAIDs), according to new data from clinical and epidemiological studies.

1. Piroxicam **should no longer be used for short-term treatment of painful or inflammatory conditions**, although it may still be prescribed for symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. However, even for these conditions, **it should not be used as first-line therapy**.
2. The initial prescription of piroxicam should always be started by a physician experienced in treating inflammatory or degenerative rheumatic conditions at the lowest possible dose (**not higher than 20 mg per day**) and for the shortest period of time. In any case, the treatment should be **reviewed 14 days after initiation**.
3. An association with a **gastroprotective agent** should always be considered.
4. Piroxicam **should not be prescribed to patients with increased susceptibility** to adverse reactions, especially with a past history of GI conditions with bleeding, or skin reactions associated with other medicines.
5. Piroxicam should **not** be prescribed in association **with other NSAIDs or with anticoagulants**.

These restrictions do not apply to medicinal products containing piroxicam for topical (skin) use only.

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)

Nelfinavir
Withdrawal of all batches

Recent batches of nelfinavir mesylate, the active ingredient in Viracept®, were found to be contaminated with considerable levels of **ethyl mesylate**, a known **genotoxic** (harmful for DNA). This medicine has been withdrawn from the market by its manufacturer (Roche) to which all available packages have also been sent back. Every patient in the EU who was on Viracept® should receive an alternative antiretroviral agent. Detailed information on what has so far been done can be found at (in Portuguese):

http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_QUALIDADE/Recolha%20do%20Medicamento%20Viracept1
and
http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_SEGURANCA/Plano%20de%20ac%E7%E3o%20na%20sequ%EAncia%20da%20recolha%20do%20medicamento%20Vira.M .

Since patients who have been treated with Viracept® may have been exposed to ethyl mesylate, Roche is preparing a **registry of patients** for which the collaboration of all prescribing physicians has been requested. Two registries are being set up:

- A registry of all patients who have been exposed to product manufactured from highly contaminated batches. The latter were released in France, Germany, Italy, Portugal, Spain and the UK in March 2007 until market withdrawal in June 2007.

- Another registry to include women who took the medicine while pregnant, and children who received Viracept® or who were exposed *in utero*. This registry must include all patients treated with Viracept® since it was first placed in the market within the EU (1998).

EMEA has requested Roche to set up the registries with help from each member state's medicines authority. **Every patient included in either registry must be followed up by their doctor at 6-month intervals for a minimum of 5 years**.

Medicinal Plants from A to Z
described adverse reactions

- **Fennel** *(Foeniculum vulgare)*
  - photodermatitis, contact dermatitis, and cross reactions
  - hallucinations and seizures (oil)

Nº of Medline citations: 7

Main uses described: spasmolytic, lactation stimulant, inducer of menses, libido stimulant

- **Gentian (yellow)** *(Gentiana lutea)*
  - dyspepsia, nausea, vomiting
  - intolerance in pregnancy and in hypertensive patients

Nº of Medline citations: 1

Main uses described: appetite stimulant

- **Ginger** *(Zingiber officinale)*
  - central nervous system depression (in excessive doses)
  - potentiation of anticoagulation (in excessive doses)

Nº of Medline citations: 18

Main uses described: prophylactic of nausea and vomiting in pregnancy and motion sickness, antidyspeptic, appetite stimulant, antitussic, anti-inflammatory, spasmolytic

- **Guava** *(Psidium guajava)*
  - possible depression of cardiac inotropism (caution when used in heart patients)
  - possible potentiation of the effect of hypoglycaemic agents

Nº of Medline citations: 2

Main uses described: antiseptic for diarrhoea and inflammation of mouth and throat

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 therapeutical 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".