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Editor's Notes

One often uses expressions and even nosological nomenclatures whose accuracy will not hold on closer reflection. A good example of such is the relatively unspecific use of "anaphylactic reaction" to actually mean an anaphylactoid reaction or an ADR of a diverse nature. Another example is the use of frequency modifiers (e.g., "very frequent", "rare", etc) to describe the relative incidence of adverse reactions.

Also in this issue safety warnings concerning medicinal products used in such diverse conditions as diabetes, multiple sclerosis, multiple myeloma, hepatitis B, and haemophilia.

Rosiglitazone caution in ischaemic conditions

EMEA has recommended that the SPC and Information Leaflet of all antidiabetic medicines containing rosiglitazone be updated in order to include the following:

- a new warning against using this medicinal product in patients with **cardiac ischaemic disease and/or peripheral arterial disease**

- a new contraindication in patients with **acute coronary syndromes,** such as angina or some types of myocardial infarction, since rosiglitazone was not submitted to controlled clinical trials in this specific group of patients.

These changes resulted from a reassessment of the benefit-risk ratio of rosiglitazone and pioglitazone conducted by the CHMP in October 2007 (see former issue of the Boletim). It was then concluded that the **benefits of these antidiabetic medicines still outweigh the risks** when used within the approved indications, but information regarding rosiglitazone should be altered.

The CHMP and its Efficacy Working Party, taking into account the need for a global vision of the cardiovascular risk associated with the use of antidiabetics, are in the process of reviewing the clinical research guidelines for this field.

More information at the EMEA site:
http://www.emea.europa.eu/pdfs/human/press/pr/4223208en.pdf

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

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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, 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

Recombinant Factor VIII risk of development of inhibitor antibodies

Recombinant Factor VIII (FVIII) products are used for preventing and treating bleeding in patients with haemophilia A (congenital Factor VIII deficiency). One of the main complications of therapy is insufficient control of bleeding associated with the formation of inhibitor antibodies against Factor VIII. The **risk of developing inhibitor antibodies is higher in patients with severe haemophilia A** comparatively to those with mild or moderate disease.

The development of inhibitors in patients who are treatment naif should be viewed as a normal response of the immune system to a foreign protein. However, the development of inhibitors in previously treated patients who have received multiple transfusions and who are stable, may be related to the use of recombinant Factor VIII.

The results of a preliminary evaluation of recombinant Factor VIII products were disseminated by INFARMED in 2005. At the time it was deemed necessary to set up an expert workshop on Factor VIII and the development of inhibitor antibodies. The conclusions of this workshop which took place in 2006 were made available at:

http://www.emea.europa.eu/pdfs/human/bpwg/12383506en.pdf.

The evaluation of all data available since 2003 has recently been concluded by EMEA. Main highlights:

- According to current data, it is not possible to estimate and compare the incidence of inhibitors among the various medicinal products with recombinant Factor VIII.
- There is a tendency for low titers of FVIII inhibitors to recur after a recombinant FVIII product is substituted for another in patients previously treated with over 100 days of exposure. Since in only a few cases was it known that the patients had no inhibitors before substitution, it is not possible to conclude whether this observation results from actual recurrence or rather from closer monitoring of patients following substitution.
- There is no need to change the current treatment regimes with recombinant FVIII products. Nevertheless, the following warning has been included in section 4.4 of the SPC of every recombinant FVIII medicinal product:

  "Cases of recurrence of inhibitors (low titers) after switching medicinal products with recombinant factor VIII were observed in patients previously treated with over 100 days of exposure with a history of development of inhibitors".
- Collaboration between patients and haemophilia centres is important for detecting and recording all the data on the development of inhibitors in haemophiliac patients. Health professionals and patients should contribute towards obtaining more robust data on the incidence of FVIII inhibitors, by participating in both recording and post-marketing vigilance programs, according to the latest recommendations and guidelines.
- **Medicinal products with plasma-derived FVIII have not been evaluated,** so no conclusion can be reached regarding the occurrence of inhibitors associated with their use.

Patients should continue their treatment and follow their physician's recommendations. Should bleeding not be controlled with the usual doses of medicine, patients should see their doctor immediately.

Natalizumab liver function monitoring

Natalizumab (Tysabri®) is a selective immunosupressing agent used in the treatment of **multiple sclerosis with exacerbation-remission,** that is, characterised by alternating symptomatic and asymptomatic periods. It is indicated in patients with high disease activity inspite of treatment with beta-interferon, or when the disease is severe and evolving rapidly.

New warnings (EMEA) on liver injury to be included in the RCM and PIL of Tysabri®:

- It is adviseable to monitor the liver function of patients undergoing this treatment.

- Patients with signs of liver injury such as jaundice or choluria should see their doctor promptly.

Bortezomib contraindicated in diffuse infiltrative pulmonary disease and in pericardial disease

Velcade®, active ingredient bortezomib, is indicated for the treatment of **multiple myeloma in progression** in patients who have received more than one previous therapy and who have already been or cannot be submitted to bone marrow transplantation. EMEA has concluded that the benefits of this medicine outweigh its risks, except in patients with acute diffuse infiltrative pulmonary disease or with pericardial disease in whom this drug is contraindicated.

Before therapy with Velcade® is iniated in a patient for the first time, a **chest X-ray** should be obtained, and the **individual benefit-risk profile** considered.

Telbivudine risk of peripheral neuropathy

Sebivo® (telbivudine) is indicated as monotherapy for the treatment of **chronic hepatitis B** in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum levels of alanine aminotransferase (ALT), and histological evidence of active inflammation and/or fibrosis. EMEA has recommended that new warnings be included in the information on Sebivo®, aiming to make physicians aware of the risk of peripheral neuropathy in patients with chronic hepatitis B treated with this medicinal product (which is not yet being marketed in this country).

Cases of peripheral neuropathy in patients treated with telbivudine as monotherapy have been infrequently reported. In one clinical trial on combination therapy with telbivudine (600 mg qd) and peginterferon alpha–2a (180 µg weekly), an increased risk of peripheral neuropathy was observed. The latter cannot be excluded when using other alpha interferons (peg or standard). Furthermore the benefit of this combination has not yet been established.

Doctors should carefully follow their patients for signs of peripheral neuropathy and reconsider their treatment options should this complication supervene.

Hypersensitivity reactions to Drugs
a few tips…

Anaphylactic or anaphylactoid?

Anaphylactic reaction

Results from the release of endogenous chemical mediators triggered by a reaction between cell surface IgE antibodies and an antigen that has been reintroduced, that is, in a context of a **second contact** with the antigen (a medicine, for instance). By definition there can be no anaphylactic reaction on first exposure to a drug. This type of ADR usually occurs at the beginning of a second or subsequent exposure to a medicinal product, sometimes years after first contact, in most cases arising **between a few minutes up to two hours** following oral or parentheral administration. However, cases have been described in the middle of an initial treatment course.

Shock occurring on a first exposure to a given medicine results from an **idiosyncratic** reaction or, possibly, from **cross allergy.**

Anaphylactoid reaction

These are reactions that are usually induced by medicines and which are related to release of the same chemical mediators, only **without IgE** antibody mediation.

How severe is a hypersensitivity reaction?

In its milder forms, it affects the skin and subcutaneous tissues only: generalised rash, urticaria, periorbital oedema or angioedema. In the more severe cases, there is respiratory, cardiovascular or gastrointestinal compromise: dypnoea, wheezing, stridor, nausea, vomiting, dizziness/feeling faint, diaphoresis, chest tightness, abdominal pain… eventually evolving to collapse and loss of consciousness.

Is it angioedema?

Key-points:

- Sudden, localised and reversible oedema of the deep dermis, hypodermis and/or mucosae.
- More frequent in face, lips, hands, feet, genitals.
- Solitary or multiple locations, sometimes asymmetrical.
- May occur simultaneously or alternating with urticaria.
- Eventually, abdominal pain, vomiting and/or diarrhoea.

Is the shock anaphylactic?

The presence of signs of allergy – **urticaria, rash, angioedema, asthma-like dyspnoea** suggests anaphylactic shock, and helps to differentiate it from other types of shock, such as from cardiac failure (cardiogenic shock) or from decreased circulating blood volume (hypovolaemic shock). However, the absence of signs of allergy in the skin and mucosae does not exclude anaphylaxis.

On the other hand, should the patient present with **tachycardia** (accelerated heart rate), vasovagal syncope ("faint") can be in principle excluded, since the latter characteristically causes bardycardia (slow heart rate)

A useful web resource:

http://www.allergyclinic.co.nz/guides/12.html

Benahmed S, Picot M-C, Dumas F, Demoly P. Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Arch Intern Med 2005;165:1500-5.

Benichou C Ed. Adverse drug reactions – a practical guide to diagnosis and treatment. John Wiley & Sons; Chichester 1994.

Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371-6.

Zampino MR, Corazza M, Virgili A. Drug-induced non-histaminergic angioedema. G Ital Dermatol Venereol 2004;139:31-46.

How frequent, how rare na ADR?*

Very common: ≥1 case per every 10 exposed
Common: ≥1/100 but <1/10
Uncommon: ≥1/1,000 but <1/100
Rare: ≥1/10,000 but <1/1,000
Very rare: <1/10.000

*MedDRA frequency convention

What should one report?

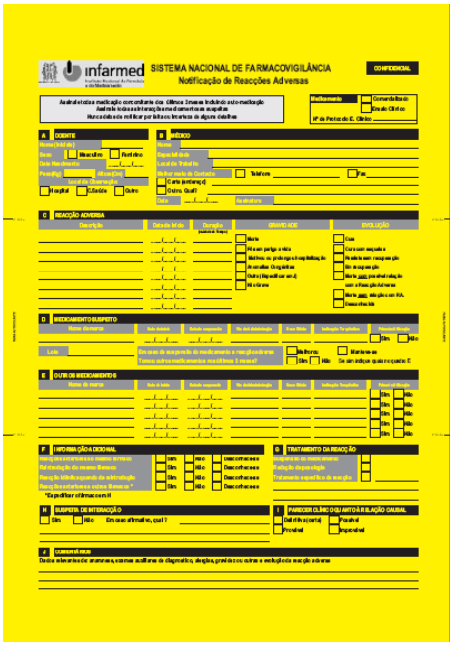
Every suspected serious adverse reaction, even if already previously described. Seriousness criteria include:

- 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

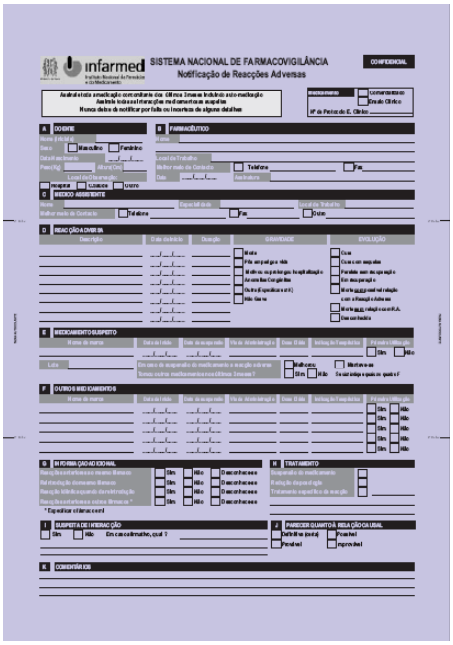
Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)

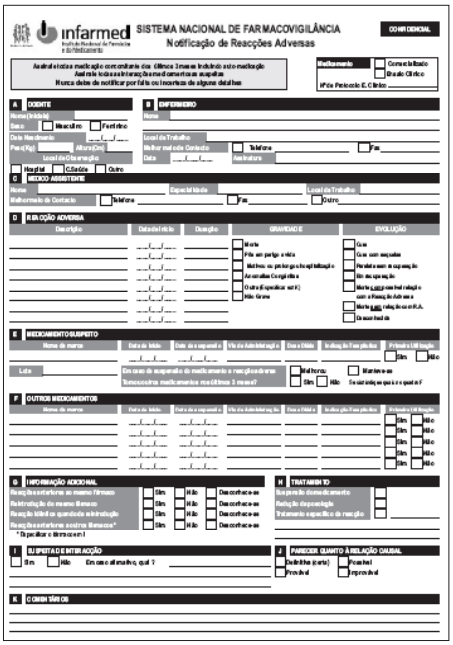
DOCTORS' YELLOW
ADR REPORTING CARD



PHARMACISTS' PURPLE
ADR REPORTING CARD



NURSES' WHITE
ADR REPORTING CARD



Medicinal Plants from A to Z

described adverse reactions

- **Pau d'Arco** *(Tabebuia avellaneade)*
  - Possible interaction with anticoagulants (increased effect)

Nº of Medline citations: 3
Main uses described: immunomodulator, cytotoxic, antibacterial, anti-fungal

- **Lemon** *(Citrus limon)*
  - erosion of tooth enamel

Nº of Medline citations: 23
Main uses described: antioxydant, microbicide; hypocitraturic calcic nephrolithiasis

- **Mallow** *(Malva sylvestris)*
  - abortive?

Nº of Medline citations: 1
Main uses described: antiinflammatory, laxative

- **Pawpaw** *(Carica papaya)*
  - abortive?
  - contact dermatitis

Nº of Medline citations: 5
Main uses described: digestive, antihelminthic, diuretic, emollient, laxative

- **Passion flower** *(Passiflora alata)*
  - hypotension
  - potentiation of sedative effects of medicines, CNS depression (high doses)
  - interaction with anticoagulants and IMAOs

Nº of Medline citations: 4
Main uses described: sedative, sleep inducer, antispasmodic, analgesic

- **Horehound** *(Marrubium vulgare)*
  - cardiac dysrhythmia (high doses)
  - dyspepsia

Nº of Medline citations: 1
Main uses described: vasodilatator, diuretic, antihelminthic

- **Yarrow** *(Achillea millefolium)*
  - contact dermatitis

Nº of Medline citations: 5
Main uses described: haemostatic, hypotensive, antidyspeptic, haemorrhoids

- **Maize, corn** *(Zhea mays)*
  - hypotension (diuresis), hipokalaemia

N.º citações Medline: 83
Main uses described: diuretic, uricosuric, antispasmodic

- **Blueberry** *(Vaccinium myrtillus)*
  - ?

Nº of Medline citations:
Main uses described: antidiarrhoeal, bactericidal, hypoglicaemic

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".