



Editor's Notes

The sulphonylurea pharmacological group includes a number of very commonly used oral antidiabetic drugs, whose safety information is undergoing a change to underscore the need for special precaution in patients with G6PD deficiency. This enzyme is necessary for red blood cell viability and its lack is associated with a genetic condition also known as favism, which affects almost half a billion people worldwide, mostly around the Mediterranean Basin, in the Middle East, tropical Africa, and tropical and subtropical Asia. According to the WHO (World Health Organisation), circa 0.39% of the European population has this recessive, x-linked hereditary deficiency.

The clinical manifestations of favism depend on the disease's variant as well as on the degree of residual red blood cell enzyme activity – from up to about 40% to as little as 1%. The most characteristic manifestation is haemolysis which, although rare, often is acute and induced by oxidative stress associated with infection, medicines, or certain foods such as fava beans, quinine-containing beverages, or products with very high vitamin C content. Each individual's tolerance to those triggers is variable and essentially unpredictable.

The French medicinal products safety agency (AFFSAPS) generically defines four categories (below) according to the risk level of haemolysis in subjects with G6PD deficiency (more commonly used medicines in bold print).

Use Contraindicated

- **Nalidixic acid**
- Dapsone
- **Metamizole sodium**
- **Nitrofurantoin**
- Rasburicase
- Sulfadiazine (oral)
- Sulphafurazole
- Sulphaguanidine
- **Sulphamethoxazole** (oral and parenteral)
- **Sulfasalazine**
- **Trimethoprim** (oral and parenteral)

Use Unadvisable, except in special conditions (cases of acute haemolysis described)

- **Ciprofloxacin** (oral and parenteral)
- Chloroquine
- Dimercaprol
- **Spiramycin** (oral and parenteral)
- Phytomenadione (vitamin K1)
- **Glibenclamide**
- **Levofloxacin** (oral and parenteral)
- **Norfloxacin** (oral)
- Sulfadiazine (topical)

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMA	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/reacoes_adversas/fichas_notificacao/index.html

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Use Unadvisable, except in special conditions (high risk pharmacological class, or potential risk of haemolysis)

- Pipemidic acid
- Carbutamide
- Enoxacin
- Phenazone (topical)
- Flumequine
- **Glibornuride**
- **Gliclazide**
- **Glimepiride**
- **Glipizide**
- **Hydroxichloroquine**
- **Lomefloxacin**
- **Moxifloxacin**
- **Ofloxacin** (oral and parenteral)
- **Pefloxacin** (oral and parenteral)
- **Prilocaine**
- Quinine
- Sulfacetamide
- Sulphadoxine
- Sulphamethizole

Use in high doses inadvisable

- **Acetylsalicylic acid**
- **Ascorbic acid**
- Benorilate
- Calcium carbasalate
- **Paracetamol**

Use possible after analysis of available data (literature and pharmacovigilance)

- **Methylene blue** (buccal and ophthalmic)
- **Bupivacaine**
- **Ciprofloxacin** (auricular and ophthalmic)
- **Cloranfenicol** (ophthalmic)
- **Colchicine**
- Diethylamine
- Dihydroquinidine
- Dimenhydrinate
- Doxorubicin
- **Streptomycin**
- *Pterodon emarginatus*
- Phenazone (auricular)
- Phenylbutazone
- Phenytoin
- **Isoniazide** (oral and parenteral)
- **Levodopa**
- **Mefloquine**
- **Nitric oxide**

- ▶ • Morpholin
- Nitroglycerin
- Nitroprussiate
- Norfloxacin (ophthalmic)
- Ofloxacin (auricular and ophthalmic)
- Para-aminosalicylate sodium (PAS)
- Pyrimethamine
- Probenecid
- Proguanil
- Propylene glycol
- Quinidine
- Succimer
- Thiamphenicol
- Trihexyphenyldil

As far as other products are concerned, the consumption of the following is generally contraindicated:

- fava beans, in whatever form
- quinine-containing beverages
- vitamin C based food supplements

The following should be used in moderate amounts:

- foods, namely fruit, with very high intrinsic vitamin C content
- beverages or concentrates with vitamin C added (maximum 1 g per day)
- according to some authors also: red wine, pulses in general, blueberries and soy-based products

Other products that may pose a potential risk according to some authors:

- medicinal herbs such as *Acalypha indica* and *Copsis chinensis*
- naphthalene (namely in mothballs)
- Henna, used as an antiseptic for wounds and tattoos

Useful resources on the net:

French medicinal product agency's site (in French):

http://afssaps.sante.fr/pdf/5/g6pd_index_sub_actives.pdf

Vigifavisme site (in French and English):

<http://www.vigifavisme.com/en/medicaments.html>

G6PD Deficiency Association site (in Italian and English):

<http://www.g6pd.org/favism/english/index.mv>

Single author site with useful external link hub (in English):

<http://www.rialto.com/g6pd/>

Sulfonylureas in G6PD-Deficient Diabetics Increased Risk of Haemolytic Anaemia

G6PD (glucose-6-phosphate dehydrogenase) is essential for hydrogen peroxide elimination. In patients who lack this enzyme, erythrocyte hydrogen peroxide is periodically increased, so the risk of haemolysis is greater in these patients. On the other hand, the pharmacological class of sulfonylureas is also associated with red blood cell oxidative stress in G6PD-deficient individuals, which explains why the risk of haemolytic anaemia associated with these drugs is much higher.

The SPC/PIL of sulfonylureas will include a **warning** in section 4.4. (Warnings and special precautions for use), so that these medicines will be given cautiously to patients with G6PD deficiency. In fact, **opting for an antidiabetic medicine from another pharmacological group** should be considered.

Moxifloxacin (Avelox® / Proflox® / Actira®*): Serious Liver and Skin Reactions

Moxifloxacin is a fluoroquinolone that is indicated for the treatment of acute exacerbations of chronic bronchitis, community acquired pneumonia, and acute bacterial sinusitis.

The effects of moxifloxacin on liver function and the occurrence of Stevens-Johnson Syndrome (SJS) are well known and referred to on the product's SPC. A review was recently conducted of serious

(including fatal) cases of liver toxicity and SJS and toxic epidermal necrolysis (TEN) type skin reactions reported for moxifloxacin worldwide.

Liver lesions that were possibly moxifloxacin related were more frequently of the **cholestatic or mixed type** than of the hepatocellular type. Symptoms usually **started 3 to 10 days into** treatment. Isolated cases of late liver toxicity were also identified which occurred almost always 5 to 30 days after discontinuation of therapy with moxifloxacin. Of the fatal liver cases, eight were considered to be possibly related to therapy with moxifloxacin. Cases of **positive rechallenge** provided additional evidence of a causal relationship. Most patients with severe liver injury on whom data concerning their outcome could be obtained, did improve or recover.

Toxic epidermal necrolysis (TEN) was reported in several cases (two of which were fatal), their causality being classified as possible. Additionally, a total of 35 cases of SJS were reported, three of which were fatal and seven life threatening. Out of a total of 10 serious cases of SJS, progression from SJS to TEN was documented in three patients.

Although these reports do not allow for definitive frequency calculations, based on the broad population exposed one can estimate that **incidence should be very low**, both for life-threatening liver injury and TEN.

From the evaluation of adverse reactions associated with the use of moxifloxacin, the following information and recommendations have resulted:

- Treatment with moxifloxacin is associated with a risk of developing fulminating, life-threatening hepatitis, as well as with a risk of life-threatening skin reactions of the Stevens-Johnson (SJS) or toxic epidermal necrolysis (TEN) type.
- Due to limited clinical data, moxifloxacin is contraindicated in patients with liver failure (Child Pugh C) and in patients with transaminase increases greater than 5-fold.
- Patients should be advised to discontinue therapy and see their doctor at the very earliest signs and symptoms of these reactions.

When prescribing moxifloxacin, recommendations on the appropriate use of antibacterial agents should be given consideration, especially in what regards the treatment of less serious infections.

The SPC and PIL of medicinal products containing moxifloxacin can be found online (in Portuguese) at:

<http://www.infarmed.pt/infomed/inicio.php>

*Currently not marketed in Portugal.

Precautions with Heparin contaminated with Hypersulphated Chondroitin Sulphate

Heparins are used for the prevention and treatment of thromboembolism in patients with a history or at risk of myocardial infarction, in patients submitted to major surgery, as well as in patients undergoing haemodialysis.

The European Medicines Evaluation Agency – EMEA – has assessed the risks associated with the use of medicinal products containing heparin contaminated with hypersulphated chondroitin sulphate:

- Hypersulphated chondroitin sulphate was detected both in standard, non-fragmented heparin, and in low molecular weight heparin (LMWH).
- There is a relation between contamination with high levels of hypersulphated chondroitin sulphate and the observation of serious undesirable effects in some patients who have received contaminated standard heparin.

All batches of contaminated standard heparin have been tagged by regulatory agencies worldwide and withdrawn from the market. On

the other hand, low levels of hypersulphated chondroitin sulphate were found in some batches of enoxaparin, a low molecular weight heparin. However, when enoxaparin was used the above undesirable effects were not observed. Withdrawing every medicinal product containing enoxaparin from the market would have led to stock depletion thus leaving patients without a treatment. EMEA has concluded that physicians may temporarily go on using enoxaparin with low levels of hypersulphated chondroitin sulphate when treating their patients and until this matter is resolved. Nevertheless, in order to minimise the risk of undesirable effects, one should:

- Avoid administering enoxaparin intravenously or intraarterially.
- Closely monitor patients for signs of allergy.
- Avoid giving enoxaparin to pregnant women whenever alternatives or non-contaminated enoxaparin are available.

Further details on the EMEA site at:

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/heparin/27772208.en.pdf>

Abacavir Association with Increased Risk of Myocardial Infarction?

Abacavir is a nucleoside analog reverse transcriptase inhibitor (NRTI) indicated for antiretroviral therapy against HIV in association with other drugs. In the European Union this product is available in stand alone form, in association with lamivudine, and in association with both lamivudine and zidovudine.

The D.A.D. study is a prospective, observational study currently including over 33,000 patients in Europe, Australia and the USA. It was launched in 1999 to determine whether there is an association between anti-HIV medicines and an increased risk of cardiovascular disease. Results suggest that the use of abacavir during the preceding six months is indeed associated with an increase in the risk of myocardial infarction. The level of risk did not seem to significantly rise in patients who had discontinued therapy 6 months before or earlier. A similar association was found with the NRTI didanosine. In an analysis of 54 clinical trials with abacavir conducted by the MA Holder - corresponding to approximately 10,000 patients -, no increased risk of myocardial infarction was observed.

EMEA has recently concluded that the currently available data do not allow for a possible association to be reliably determined between administration of abacavir and increased risk of myocardial infarction. It has requested further data from epidemiological studies to clarify this safety issue. In the meantime, patients should continue taking their medicines and address their physician if necessary. Measures should be taken to minimise or control modifiable risk factors, such as smoking, high blood pressure, hyperlipaemia, and diabetes mellitus.

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.

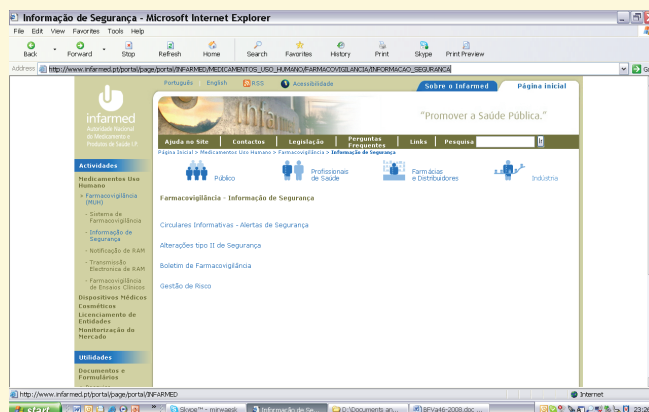
Every suspected **increase in the frequency** of ADRs (both serious and non-serious)

Safety Information Online

Medicinal products safety information update highlights can now be found concentrated on a single Infarmed I.P. online page (in Portuguese). Go to:

http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA

The following page with four main links will open:



The "Circulares Informativas – Alertas de Segurança" (Circular Letters – Safety Alerts) link gives you access to alerts which are organised chronologically by year and, within each year, by date of issuance and type of alert (e.g.: regarding a medicine, a medical device, or a cosmetic product).

On "Alterações tipo II de Segurança" (Type II Safety Variations) safety measures are described which entail updating information contained in the SPC or PIL of those medicines for which a potential safety problem has been identified. A clinically relevant example is published in this issue of the Boletim (next page) – a safety variation concerning antidepressants.

The third link takes you directly to the Boletim de Farmacovigilância online:

BOLETIM ONLINE ADDRESS WITH ALL ISSUES SINCE 1998 :

www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH

Finally, regulatory matters, background and guidelines regarding "Risk Management" can be accessed through the fourth link. Risk management associated with the use of medicines aims to optimise their benefits whilst minimising their risks. This is an ongoing and dynamic process, which starts at the stage of medicinal product development and follows through its whole life cycle. It is characterised by a series of activities and interventions whose purpose is to identify, characterise, prevent, or minimise the risks associated with the use of medicinal products.

Useful contact points:

- Centro de Informação do Medicamento e Produtos de Saúde (CIMI) do INFARMED. Ph.: 21 798 7373. E-mail: cimi@infarmed.pt
- Direção de Gestão do Risco de Medicamentos. Ph: 21 798 7140. E-mail: info.seguranca@infarmed.pt.

Antidepressants: New Information on the SPCs* Warnings and special precautions for use Undesirable effects (Sections 4.4. and 4.8.)

Suicide/suicidal ideation/worsening of clinical condition

Depression is associated with an increased risk of suicidal ideation, auto-aggressivity, and suicide (suicide-related thoughts or behaviour). This risk remains until significant symptom remission occurs. Since no significant improvement may be evident during the **first few weeks or so of treatment**, patients should be more carefully monitored until clinical improvement occurs. According to common clinical practice, the risk of suicide in general can **increase during the initial stages of recovery**.

Other psychiatric disorders for which some of these medicines may eventually be prescribed can be themselves associated with an increased risk of suicide related ideation/behaviour. Additionally, these conditions may be co-morbid with major depressive disorders. Consequently, in the treatment of **patients with other psychiatric disorders the same precautions should be taken** as when treating patients with major depressive disorders.

Patients with a history of suicide related thoughts/behaviour who present with these symptoms to a significant degree before therapy is started, are also at higher risk of suicidal ideation or attempted suicide, and should therefore be carefully monitored during treatment. A meta-analysis of placebo-controlled clinical trials conducted in adults with psychiatric disorders has shown an increase in the risk of suicide related behaviour in patients younger than 25 years who were taking antidepressants comparatively to patients on placebo. Drug therapy should be intensively monitored, especially in higher risk patients at **the initial stages of treatment** and following any **changes in dosage**.

Patients and caregivers should be reminded of the need for looking closely for any worsening of the clinical condition, suicide related thoughts/behaviour, and they should be advised to seek medical care should any of the above supervene.

The frequency of suicidal ideation/behaviour with these drugs is not known.

Antidepressants: New Information contained in the PILs*

Suicide related thoughts and worsening of your depression or anxiety disorder

If you are depressed and/or have an anxiety disorder, you may sometimes think of harming yourself or even committing suicide. These thoughts may increase at the beginning of antidepressant therapy, since antidepressants require some time to have an effect. Therapeutic effects usually take about two weeks to be felt but it may sometimes take longer.

You may be especially predisposed to this type of thoughts in the following situations:

- If you have a history of thoughts of suicide or self-harm.
- If you are a young adult. Data from clinical studies has shown a higher risk of suicidal behaviour in adult individuals younger than 25 years with psychiatric disorders treated with antidepressants.

Should you, at any moment, experience thoughts of self-harm or suicide, you should contact your physician or go to hospital immediately.

It may be useful for you to tell someone close or a relative that you are depressed or have an anxiety disorder, and to have them read this leaflet. You may also want to ask them to inform you should they detect any worsening of your depressive or anxiety condition, or should they be concerned with changes in your behaviour.

See INFARMED site: *Alteração de Segurança - Risco de suicídio* (March 2008)

amitriptyline, citalopram, clomipramine, dosulepine, duloxetine, escitalopram, fluoxetine, fluvoxamine, Hypericum perforatum, imipramine, maprotiline, mianserine, milnacipran, mirtazapine, moclobemide, nortriptyline, paroxetine, pirlindol, reboxetine, sertraline, tianeptine, trazodone, trimipramine, venlafaxine.

*Translated and adapted from the Portuguese text.

Medicinal Plants from A to Z described adverse reactions

• **Nutmeg** (*Myristica fragrans*)

- hallucinations (toxicity when ingested in quantities greater than about 5 g)

Nº of Medline citations: 9

Main uses described: spasmolytic, CNS stimulant

• **Seed-under-leaf** (*Phyllanthus niruri*)

- abortifacient (in high doses)

Nº of Medline citations: 2

Main uses described: urinary stones, diuretic, liver protection

• **Lion's ear** (*Leonotis nepetaefolia*)

- abortifacient?

Nº of Medline citations: 1

Main uses described: anti-inflammatory, spasmolytic, uricosuric

• **Rhubarb** (*Rheum palmatum*)

- abdominal colic
- hyponatraemia, hypokalaemia, hypocalcaemia
- anaphylaxis
- genotoxicity?
- interference in the absorption of iron and other minerals

Nº of Medline citations: 6

Main uses described: appetite stimulant, laxative (antidiarrhoeal - in low doses), anti-infective, 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 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".