

From the Director

Spontaneous adverse drug reaction reporting remains one of the main pharmacovigilance tools significantly contributing towards the detection of ADRs once medicines are in the market.

The Portuguese National Pharmacovigilance System has since its inception in 1992 consistently had a growing number of annual reports. The figure was indeed four-fold higher in 2011 than it had been in 2000. Underreporting however is still a significant limitation.

Recently, European legislation has been passed to reinforce the competencies and roles of pharmacovigilance. Some major changes are expected as a consequence, the active participation of patients through suspected ADR reporting being one of the most significant and with the most potential impact on health professionals and the pharmacovigilance system at large.

In an endeavour to facilitate spontaneous reporting nationwide, Infarmed has developed a new tool for online ADR reporting – the “Portal RAM” (ADR Portal).

Read on to learn how to access and report through this Portal. We hope this feature will further the role of health professionals within the National Pharmacovigilance System.

Online reporting of adverse drug reactions by health professionals and patients



Portal RAM for ADR reporting.
Online forms for both health professionals or patients.
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How can I report an adverse reaction?

• ADR Portal (Portal RAM):

<http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage>

• Report Card online printout link:

www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM

• Postage Paid Card

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What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
PIL	Patient Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

BOLETIM'S ONLINE INDEX AT:

http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PHARMACOVIGILANCE_BULLETIN/ONLINE_INDEX

Online reporting of adverse drug reactions by health professionals and patients

The Portuguese National Pharmacovigilance System had its kick-off in June 1992 and is now twenty years old. It has stored and processed over 20,000 ADR reports with an average increase rate of 2,000 additional reports per year. It is now able to take on the challenges of the new European pharmacovigilance legislation, a package which was published on 31-12-2012 in the Official Journal of the European Union and includes two documents: Regulation No. 1235/2010 (replacing Regulation No. 726/2004) and Directive 2010/84/EU (replacing Directive 2001/83/EC).

This new EU legislation came into force earlier this year in July and sets forth that patients should be able to take active and direct part in national pharmacovigilance systems including by being able to report ADRs. Additionally, a web-based ADR reporting tool should be made available for both patients and health professionals.

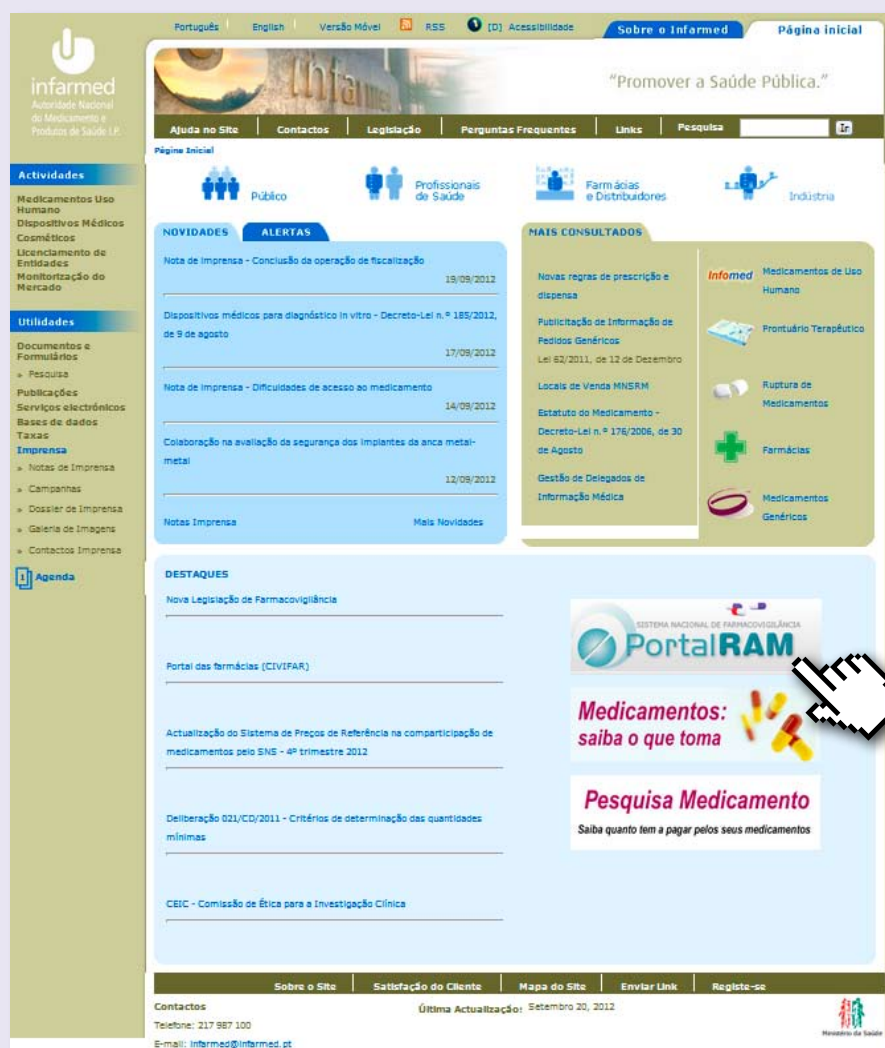
In the case of Portugal, INFARMED's new **Portal RAM** (ADR Portal) is already fully operational.

It can be accessed at Informed's website at www.informed.pt


or directly at

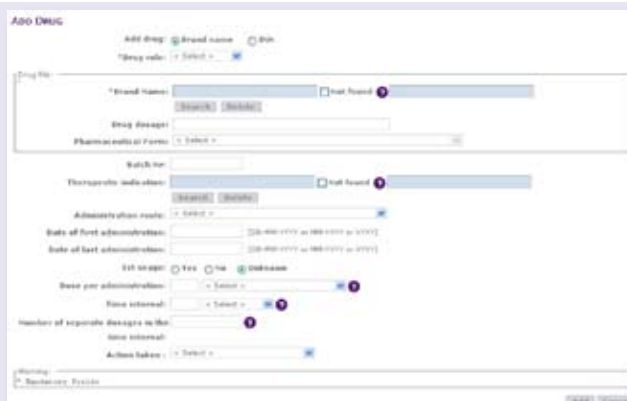
<http://extranet.informed.pt/page.seram>.

Health professionals and patients can report ADRs by simply filling out dedicated online forms.



Hard copies of reporting cards will still be accepted, and a new paper form for patients is also available for printing out from the Informed website.

The **online forms** are similar for both health professionals and patients, but for the former equally precise but less technical language is used so that laypeople may easily understand exactly the type of data required for the report to be valid and useful. In addition, and more so in the patients, form and for the more complicated fields, help bubbles highlighted with  have been inserted. A good example is the field where the drug's posology is to be entered.



Apart from ADR report submission, the Portal also provides diverse pharmacovigilance information, news and useful links. A FAQ section is included and objectives, definitions and contact details within the scope of pharmacovigilance can be found as well.



Moreover, the Portal includes National Pharmacovigilance System **internal management** features allowing for communication and information management between the Regional Pharmacovigilance Units and the system's coordinator – INFARMED itself. Reports uploaded into the Portal become automatically available for the corresponding regional unit making, report transcription and delayed transmission obsolete. The reports are then validated and processed on the Portal's platform as well. They are uploaded into the Portuguese system's database and made available for electronic transmission to the European (EudraVigilance) and the world (WHO) databases.

Although a patient or health professional who wants to report an ADR needs not **register**, this is highly recommended in that it not only prevents the reporting person from having to fill in their data every time they report a new case, but also allows them to later provide any relevant additional information pertaining to previously reported cases by the same route. Furthermore, the registered user can save the data inserted at any given moment and later come back to finalise their report without having to start over. Registered users can also access their history with every report submitted online in the past, as well as any additional data requests and replies if applicable.

How can I report an ADR on Portal RAM?

The first step to report a case of ADR on the Portal is to **select the type of form** applicable, namely health professional or patient.



In either case, **five tabs** will come on with fields that can **quickly and easily** be filled out.



The five online form tabs include each an explanation in the screen's upper right corner. They request data on the adverse reaction, the suspected medicine(s), the patient, the reporting person, as well as any additional data that may be relevant for assessing the case.

The tabs can be filled out **in any order**. The user can, for instance, start by describing the adverse reaction or by identifying the suspected medicinal product, then go on to the remaining tabs.

The reporting person has to provide a **valid email address** for any future contact on the submitted report. This ensures data processing agility and reliability. Similarly to other ADR reporting methods, all **personal data** are kept **confidential**. Once the form has been completed and in order for the entered data to be transmitted onwards, the reporting person has to tick off a confidentiality acknowledgement box.

In the data processing step that follows, the site user (whether registered or not) receives an email with a **temporary** report submission **number**. They will later get a definitive **registration number** as soon as the case has been validated. Once **causality** assessment is completed, the system communicates the corresponding ascribed category to the reporter.

Portal RAM is easy to use whenever you need to report a suspected adverse reaction. Using the portal is also a way health professionals and patients alike have to contribute to the relevance of the National Pharmacovigilance System and to protect public health through better knowledge of the safety profile of medicinal products.



Pioglitazone is indicated as oral monotherapy or as part of double or triple therapy regimes for patients who cannot be treated with metformin or who cannot reach adequate glycaemic control despite the use of maximum tolerated doses of metformin, sulphonylureas or both. Pioglitazone is also indicated in association with insulin in the treatment of adult patients with type 2 diabetes mellitus with insufficient glycaemic control with insulin and for whom metformin is not indicated on account of contraindications or intolerance.

Following a review on a possible association between pioglitazone and increased risk of bladder cancer, EMA has concluded that, although there is a small risk of bladder cancer associated with

pioglitazone, benefit still outweighs risk in a limited population of type 2 diabetics (see above and Boletim n.ºs 1 and 3/2011, and n.º 4/2007).

Several risk minimisation recommendations have been made in the meantime, to do with **careful patient selection** and **individual risk-benefit assessment**. One of the risk minimisation measures consists of an **educational package** for all the health professionals expected to be involved in pioglitazone prescription/use in Europe. This package includes a Guide, the SPC and Information Leaflets. Look out for it.

Margarida Guimarães

Interactions to keep in mind!

Patients with Erectile Dysfunction on sildenafil, tadalafil or vardenafil (vasodilator phosphodiesterase type 5 inhibitors)



Risk of orthostatic hypotension (and possible angina) with:

- nitro-derivatives such as vasodilator **nitrates**, recreational nitrates (amyl nitrite **poppers**) – potentially lethal interaction
- antihypertensive agents
- medicines with a hypotensive side effect (e.g.: alpha-blockers for benign prostate hypertrophy, baclofen, levodopa, nicotine)
- **acute consumption of alcohol**

Risk of angina also with:

- vasoconstricting agents such as:
 - triptans for migraine
 - sympathomimetic nasosinusual decongestants such as pseudoephedrine, oxymethazoline
 - dipyridamole, etc.
- agents which induce tachycardia:
 - bronchodilators: beta-agonists and theophylline
 - sympathomimetic nasosinusual decongestants
 - levothyroxine
 - minoxidil for hair loss
 - rosiglitazone and pioglitazone
 - certain antineoplastic agents (e.g., bevacizumab, rituximab, docetaxel, paclitaxel, etc.)
 - venlafaxine and imipramine antidepressants, buspirone
 - varenicline and bupropion used in tobacco addiction
 - caffeine, etc.
- beta-blocker withdrawal (chronotropic effect)

Risk of torsades de pointes

(QT-interval prolongation) with:

- various antiarrhythmic agents
- fluoroquinolones (especially moxifloxacin) and macrolides
- antifungals such as fluconazole
- antimalarials such as mefloquine
- HIV protease inhibitors
- bronchodilating beta-agonists
- anti-H1 antihistamines such as mizolastine, ebastine or rupatadine
- imipramine antidepressants, venlafaxine and citalopram
- neuroleptics
- contrast agents for magnetic resonance imaging such as gadobutrol
- etc.

Risk of potentiation of ototoxicity* with:

- potentially ototoxic antimicrobials
- loop diuretics
- platinum-derived antineoplastic agents, docetaxel...
- etc.

* including sudden irreversible deafness

Risk of potentiation of any medicines exposing to vision disorders

- special care with patients with a history of non-arteritic anterior ischaemic optic neuropathy

Risk of potentiation of dose-dependent undesirable effects through pharmacokinetic interaction with:

- cytochrome P450 isoenzyme CYP 3A4 inhibitors (in the case of sildenafil, tadalafil, vardenafil)
- cytochrome P450 isoenzyme CYP 2C9 inhibitors (in the case of sildenafil, vardenafil)

Medicines which can cause/worsen erectile dysfunction

- Antihypertensives
- Vasoconstrictors
- Inducers of peripheral neuropathy (e.g., certain antineoplastic agents, antiretrovirals, alpha interferon, tacrolimus, etc.)
- Antiandrogenic agents
- Agents with ansiogenic and mood depressing effects
- etc.

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BOLETIM ONLINE ADDRESS WITH ALL ISSUES SINCE 1998 :

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

Click on Pharmacovigilance Bulletin, then year of issue.