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This PDF is interactive. This symbol, URL's, phrases and words printed in blue have associated links.

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From the Editor

INFARMED's activities in the field of pharmacovigilance and medicines risk management is intense. It often translates into the issuance of safety communications addressed to health professionals. Permanent communication with professionals and the general public is highly dynamic and one of the most important tools for materializing the safety conclusions reached at European level into actual clinical practice.

The Boletim's last issue had a new layout and a section summarizing the latest Communications to health professionals began to be part of its regular contents. In this quarter we have yet a new additional section to let professionals know about the latest educational materials. This section is organized by alphabetical order of the trademark names of the products for which those materials have been produced, both addressing health professionals and patients. You can easily look it up and find out whether anything of relevance to your practice has come out.

Your instant access to safety communications will be further completed by bookmarking on your internet browser the following link (in Portuguese) for Safety Alerts (either recente or from the preceding years):

http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_SEGURANCA

*Also in this issue: domperidone, zolpidem, diacerein, transdermal fentanyl, and a panorama of **ADRs** reported to the Portuguese National Pharmacovigilance System in 2013.*

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Domperidone
Use restricted to minimize the risk of adverse cardiac reactions

Quick Read
Domperidone should only be used in **low doses** and to treat **nausea and vomiting**. This will help to minimize the risk of adverse cardiac reactions.

Domperidone is a dopamine antagonist with antiemetic properties. It has so far been used for various digestive problems: nausea and vomiting, bloating and dyspepsia.

The occurrence of serious adverse cardiac reactions with domperidone, including QT interval prolongation and arrhythmia, was assessed by the European Pharmacovigilance Working Party in 2011 (**Boletim de Farmacovigilância – 4th Quarter 2011**). In March 2013, the Belgian medicines agency started a safety review following new reports of cardiac reactions. This review was concluded in March 2014 and confirmed a risk of serious reactions such as **QT interval prolongation**, *torsade de pointes*, **serious ventricular arrhythmia and sudden cardiac death**. Risk is higher in patients **older than 60 years**, in adults taking **oral doses higher than 30 mg**, and in patients who are simultaneously taking medicines which prolong the QT interval or inhibit cytochrome CYP3A4.

In order for the benefits of the use of medicinal products containing domperidone to go on outweighing its known risks, health professionals should adopt the following recommendations from the **PRAC** which will be reflected on the **SmPC**s and the **PIL**s:

- The risk-benefit ratio of domperidone remains positive for treating nausea and vomiting. There is no evidence of the efficacy of domperidone in other indications, such as abdominal bloating or dyspepsia.
- Domperidone should be used at its lowest effective dose and for the shorted period of time possible. Treatment duration should not exceed 1 week.
- In adults and adolescents weighing more than 35 Kg the dose to be used is 10 mg up to three times a day orally (maximum daily dose: 30 mg). The recommended rectal dose is 30 mg twice a day.
- In children and adolescents weighing less than 35 Kg the recommended dose is 0.25 mg/Kg of body weight up to 3 times a day. To ensure dosing accuracy oral suspensions should include a measuring device.
- Domperidone is contraindicated in:
  - patients with severe liver impairment whose heart conduction is or may be compromised
  - patients with congestive heart failure
  - concomitant use of medicines which prolong the QT interval or which are CYP3A4 inhibitors.

The medicinal products which do not comply with the above new recommendations (oral medicines dosed at 20 mg; 10 and 60-mg suppositories; cinarizine + domperidone association) will be withdrawn from the market. They are no longer authorized in Portugal.

Magda Pedro

Zolpidem
Safety review

Quick Read

The hypnotic agent zolpidem maintains a positive risk-benefit ratio. However remember to use the lowest effective dose in a single dose and at least eight hours before any activity for which sleepiness or prolonged reaction times could be critical.

Zolpidem is a sleep-inducer that is similar to benzodiazepines. It has sedative properties and is indicated in insomnia which is severe, incapacitating or which causes the patient extreme anxiety. It should be used in short duration treatments.

EMA initiated a safety review of all products containing zolpidem following a number of reports of patients presenting with sleepiness and slower reactions on the day after taking the medication, leading to an increased risk of accidents in activities requiring alertness such as driving.

This review was started in July 2013 and is now **finished**: the **risk-benefit ratio of zolpidem remains positive**, but the SmPCs and PILs will be changed to include measures aimed at minimizing the risks associated with somnolence and decreased reactions on the day after taking the medication. Recommendations for health professionals:

- The daily dose of zolpidem remains **10 mg a day in adults** and 5 mg a day in the elderly and in patients with liver failure – this dose should not be exceeded. Data have shown that most of the cases of driving problems occurred with a daily dose of 10 mg. However, the use of lower doses (5 mg) was not effective and did not significantly reduce the risk associated with driving.
- Patients should take the minimum effective dose **in a single dose** before going to bed. Some studies have shown that there is an association between taking zolpidem in the middle of the night and a decrease in driving capacity the following day.
- **An interval of at least 8 hours** between taking zolpidem and activities requiring alertness (e.g., driving, operating machinery) is recommended.
- The risk of alertness reduction is potentiated by taking zolpidem in doses higher than those recommended or by taking it simultaneously with **alcohol or other substances** acting on the nervous system.

Catarina Costa

Diacerein
Start with caution

Quick Read
Diacerein to be prescribed by doctors experienced in treating hip and knee arthritis, in patients up to 65 years and without liver impairment. Start with half the dose.

Diacerein is a medicinal product used in the treatment of diseases such as osteoarthritis. Following a recommendation by EMA in November 2013 to **suspend** this medicine and a request by some MA Holders, the European agency conducted a new safety review. According to this review and in order to keep the weight of diacerein's benefits above that of its known risks, EMA and Infarmed recommend:

- Diacerein should **only** be used in the treatment of **hip and knee osteoarthritis**. It is not recommended for the treatment of rapidly progressive hip arthritis.
- Therapy with diacerein should only be started by doctors who are **experienced** in the treatment of osteoarthritis.
- Diacerein should not be used in patients with **liver disease** or with a history of liver disease. Physicians should monitor their patients' hepatic function so that they may detect any liver problems that may arise. Patients should be advised on how to recognize the early signs and symptoms of this type of conditions.
- Minimization of the risk of severe diarrhoea:
  - Do not use in patients over 65 years of age.
  - It is recomended that therapy should be started with **half the normal dose (50 mg/day) in the first 2 to 4 weeks**, after which the recommended dose is 50 mg twice a day.
  - Treatment should be interrupted in case of diarrhoea.

Margarida Guimarães

Transdermal Fentanyl
Risk of accidental exposure

Quick Read

Caution: accidental exposure, namely of children, to transdermal patches of fentanyl. Care should be exerted when choosing the application site, monitoring patch adhesion and disposing of it safely.

Transdermal fentanyl is a narcotic analgesic which can be very effective in controlling pain. It is used in adults for the relief of long-term pain in patients with cancer and of untreatable pain requiring potent medication. It is also indicated in the treatment of severe, long-duration pain in children two years or older receiving opioid therapy.

Following a safety review, **PRAC** has concluded that there is an increased risk of accidental exposure due to low **visibility** of the transdermal fentanyl **patches.** It has therefore recommended that their visibility be improved. Other risk minimization measures include changes to the **SmPC** / **PIL** and a Dear Healthcare Professional Communication (DHPC).

The Portuguese translations of the texts to be implemented can be found **here**.

Margarida Guimarães

ADR reports received by the Portuguese National Pharmacovigilance System in 2013

Quick Read

The number of ADR reports received by the Portuguese National Pharmacovigilance System grew more than 11% from 2012 to 2013. Over 21% of reports from both professionals and patients have been entered via the Infarmed online ADR Portal (Portal RAM).

A total of 3,461 suspected **ADR** reports were entered into the Portuguese National Pharmacovigilance System in 2013, of which 2,767 (80%) were serious. Compared to 2012, there was an increase in 11.5% in the number of reports received.
Chart 1 shows that in 2013, fifty-six percent of the total were sent in via the industry (indirect route) and 44% were sent in directly by health professionals and patients (direct route).

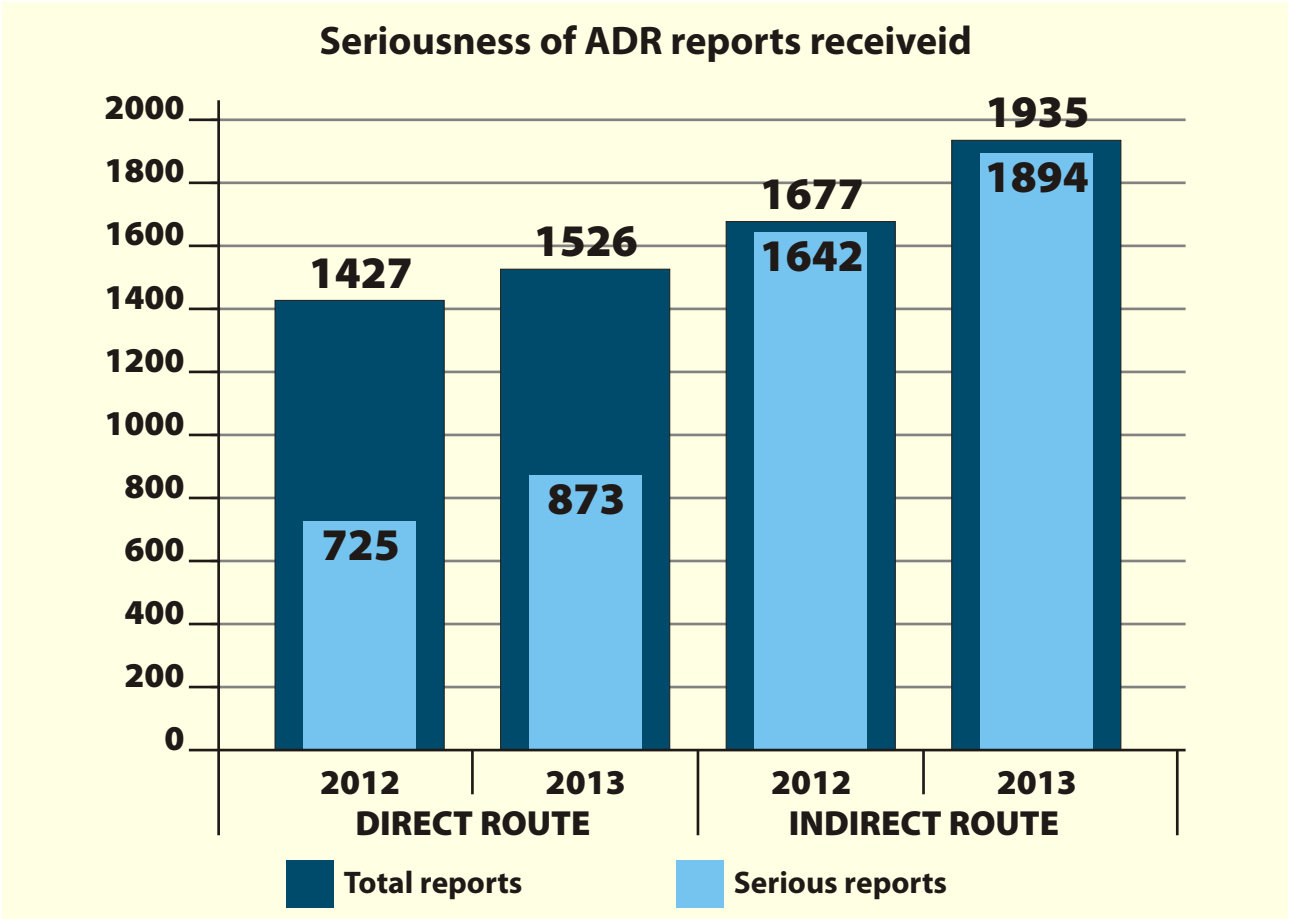

Chart 1: Absolute frequencies of ADR reports received by the National Portuguese Pharmacovigilance System in 2013 vs 2012, via the Direct (health professionals) and Indirect (industry) routes, and proportion of serious cases (N=3,461 in 2013; N=3,104 in 2012).

Continued on next page

NB:

[1] This total (3,461) includes reports (0.8%) where no actual adverse reaction occurred but which correspond to relevant safety information to be monitored (e.g., exposure during pregnancy, medication error).

ADR reports received by the Portuguese National Pharmacovigilance System in 2013

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Of the reportes entered via the direct route, reporting agents were distributed as shown in Chart 2.

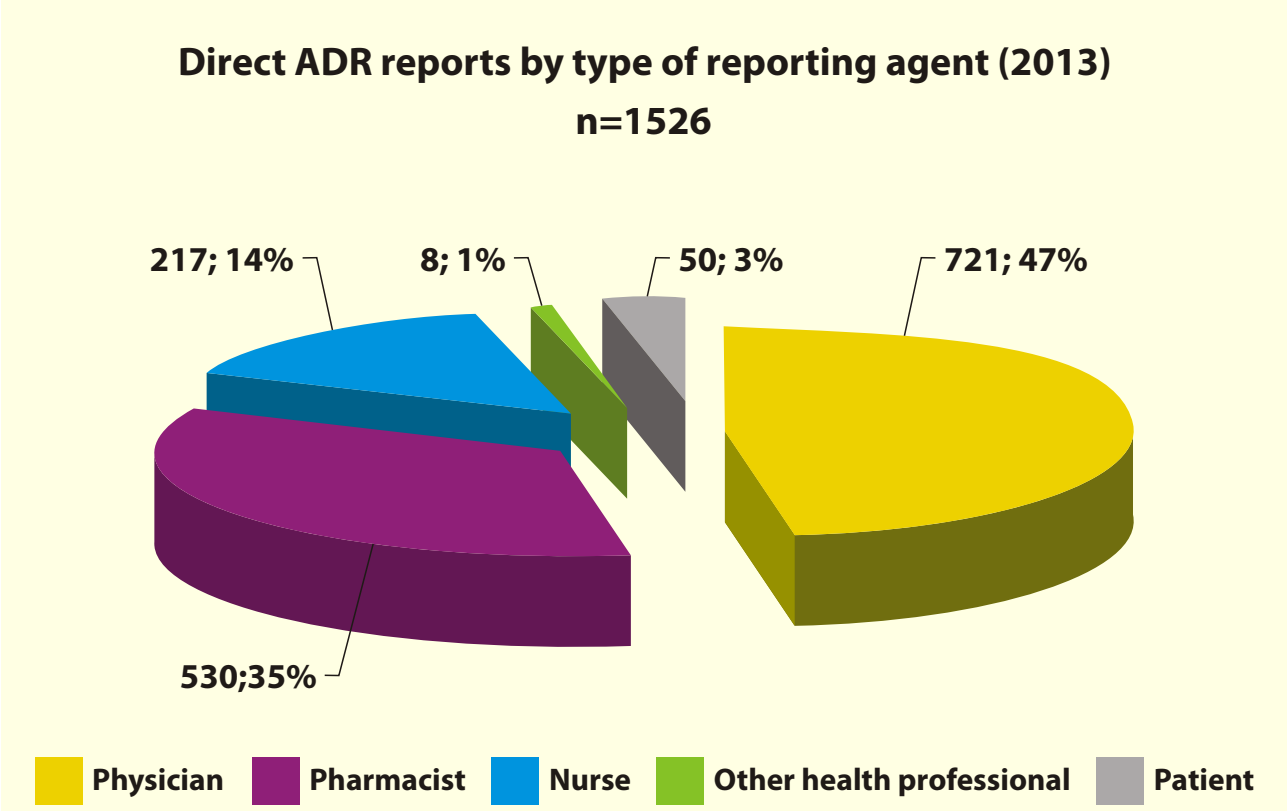

Chart 2: Relative frequency of ADR reports received by the National Portuguese Pharmacovigilance System in 2013 directly from health professionals and patients (n=1,526) – distribution by type of reporting agent.

In 2013, 1,526 **ADR** reports were received directly from health professionals and patients (vs. 1,427 in 2012). Most were entered by physicians (47%), a 10% increase in relation to 2012. Pharmacists on the other hand reported 11% less (35% in 2013). Nurses' reporting rate remained fairly stable from 2012 (15%) to 2013 (14%).

Patients sent in 3% of the total of reports directly received in 2013, which amounted to a 2% increase from 2012.

Of the 1,526 direct reports, 330 (22%) were entered online through Portal RAM (Infarmed's ADR portal). Of those 330, 93% (306) were reported by professionals, while 7% (24) were entered by patients.

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ADR reports received by the Portuguese National Pharmacovigilance System in 2013

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Fifty-six percent of the reports from professionals were "serious", which was less than the proportion of serious cases (63%) reported by patients.

Among health professionals, pharmacists accounted for 38% of online reports (34% serious), physicians 34% (73% serious) and nurses 20% (71% serious). "Other health professionals" reported only 1% of the total (50% of which were serious).

The cases

Once the duplicates (more than one reporting agente or route for the same case) were cancelled out, a total of 3,075 single cases remained, of which 78% were serious. The five SOC (System Organ Classes) that stood out in 2013 were: General disorders and administration site conditions (18%), Nervous system disorders (9%), Skin and subcutaneous tissue disorders (11%), Gastrointestinal disorders (11%), and Infections and infestations (6% each). These 5 SOCs accounted for 55% of the total and are the same as in 2012.

Suspect or interacting medicines corresponded to 74 different ATCs. Six groups only accounted for 50% of occurrences as shown in the table below.

ATC	Relative frequency 2013	Relative frequency 2012
J07 – Vaccines	12%	9%
L01 – Antineoplastic Agents	12%	12%
L04 – Immunosuppressants	10%	8%
J01– Antibacterials for Systemic Use	6%	8%
J05 – Antivirals for sistemic use	5%	6%
N06 – Psychoanaleptics	5%	3%

Leonor Nogueira Guerra, Inês Clérigo, Fátima Hergy

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Bosentano Zentiva (bosentan)	***Information for health professionals*** Guia para o prescritor com informação importante de segurança – 1.ª versão aprovada em fevereiro de 2014 ***Information for patients*** Guia para o doente com informação importante de segurança – 1.ª versão aprovada em fevereiro de 2014
Circlet (etonogestrel + ethinylestradiol)	***Information for patients*** Cartão de apoio para a doente - 1.ª versão aprovada em março de 2013
Efient (prasugrel)	***Information for prescribing physicians*** Carta para o profissional de saúde – 1ª versão aprovada em fevereiro de 2012 For cardiologists, internal medicine and family medicine specialists.
Enbrel (etanercept)	***Information for patients*** Cartão de alerta do doente – 2.ª versão aprovada em março de 2014
Eylea (aflibercept)	***Information for physicians*** Recomendações para o Médico – 2.ª versão aprovada em novembro de 2013 Pictograma de procedimento de injeção intravítrea – 2.ª versão aprovada em novembro de 2013 ***Information for patients*** Guia do Doente com degenerescência macular relacionada com a idade (DMI) neovascular (húmida) – 2.ª versão aprovada em novembro de 2013

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Ilaris (canacinumab)	***Information for physicians*** Informação importante de segurança para o médico sobre o tratamento de Síndromes Periódicos associados à Criopirina (CAPS) com Ilaris – 3.ª versão aprovada em dezembro de 2013. ***Information for patients*** Cartão de Alerta para o Doente em tratamento de Síndromes Periódicos Associados à Criopirina (CAPS) – 3.ª versão aprovada em dezembro de 2013 Guia de administração para o Doente – 3.ª versão aprovada em dezembro de 2013
Implanon NXT (etonogestrel)	***Information for health professionals*** Guia de referência – 2.ª versão aprovada em janeiro de 2013
Kadcyla (trastuzumab emtansine)	***Information for health professionals*** Informação de segurança muito importante para os profissionais de saúde que prescrevem, dispensam e administram Kadcyla – 1.ª versão aprovada em março de 2014
Leflunomida Medac (leflunomide)	***Information for health professionals*** Leflunomida medac – Folheto informativo para o médico – 1.ª versão aprovada em fevereiro de 2012 ***Information for patients*** Leflunomida medac – Folheto informativo para o doente – 1.ª versão aprovada em fevereiro de 2012
Mircera (methoxy polyethylene glycol-epoetin beta)	***Information for physicians*** Guia do médico – 2.ª versão aprovada em fevereiro de 2014

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Nebido (testosterone undecanoate)	***Information for prescribing physicians*** Como administrar Nebido® com segurança (ampolas) – 2.ª versão aprovada em abril de 2014
NeuroBloc (botulinum toxin B)	***Information for physicians*** Informação de segurança importante dirigida aos médicos – 1.ª versão aprovada em dezembro de 2013 ***Information for patients*** Guia para o doente – 1.ª versão aprovada em dezembro de 2013
Opgenra (eptotermin alfa)	***Information for health professionals*** Brochura educacional dirigida aos profissionais de saúde – 1.ª versão aprovada em fevereiro de 2014
Pradaxa (dabigatrano)	***Information for physicians*** Guia do prescritor para a prevenção do AVC em doentes com fibrilhação auricular – 6.ª versão aprovada em fevereiro de 2014 Guia do prescritor para a prevenção primária de acontecimentos tromboembólicos venosos – 6.ª versão aprovada em fevereiro de 2014
Remodulin (treprostinil)	***Information for physicians*** Carta para os profissionais de saúde – 1.ª versão aprovada em maio de 2013 Slides para formação de profissionais de saúde – 1.ª versão aprovada em maio de 2013 Estes materiais educacionais são dirigidos aos médicos prescritores de Remodulin. ***Information for patients*** Brochura para o doente – 1.ª versão aprovada em maio de 2013 Questionário para o doente – 1.ª versão aprovada em maio de 2013

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Remsima (infliximab)	***Information for prescribing physicians*** Ficha de rastreio de doentes para a terapêutica com Infliximab – 1.ª versão aprovada em dezembro de 2013 Informação de segurança importante para os médicos prescritores de Remsima (Infliximab) – 1.ª versão aprovada em dezembro de 2013 Brochura educativa para profissionais de saúde: Informação de segurança importante sobre a utilização de Remsima em crianças com doença inflamatória intestinal – 1.ª versão aprovada em dezembro de 2013 ***Information for patients*** Calendário de perfusões para o tratamento de 8 semanas a partir do 3.º ciclo – 1.ª versão aprovada em dezembro de 2013 Calendário de perfusões para o tratamento de 6-8 semanas a partir do 3.º ciclo (para doentes com espondilite anquilosante) – 1.ª versão aprovada em dezembro de 2013
RoActemra (tocilizumab)	***Information for health professionals*** Instruções passo a passo para a preparação e administração de RoActemra relativa à indicação terapêutica artrite idiopática juvenil sistémica – 5.ª versão aprovada em dezembro de 2013 Informação para o profissional de saúde relativa à indicação terapêutica artrite reumatóide – 5.ª versão aprovada em dezembro de 2013
Ruconest (conestat alfa)	***Information for health professionals*** Material educacional para os médicos prescritores – 1.ª versão aprovada em abril de 2013 ***Information for patients*** Cartão de Alerta do Doente – 1.ª versão aprovada em abril de 2013

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Simponi (golimumab)	***Information for prescribing physicians*** Informação aos médicos prescritores – 2.ª versão aprovada em outubro de 2013
Sonovue (sulphur hexafluoride)	***Information for physicians and users*** Sonovue – Material educacional/Informação para médicos e utilizadores – 2.ª versão aprovada em dezembro de 2013
Stamaril (yellow fever vaccine)	***Information for health professionals*** Informação dirigida aos profissionais de saúde – 2.ª versão aprovada em dezembro de 2013
Stelara (Ustecinumab)	***Informação para o profissional de saúde*** Informação de segurança importante para o profissional de saúde – 4.ª versão aprovada em dezembro de 2013 Instruções de utilização para o profissional de saúde – 2.ª versão aprovada em dezembro de 2013 Instruções de utilização para o profissional de saúde (brochura) – 2.ª versão aprovada em dezembro de 2013 ***Information for patients*** Informação de segurança para o doente – 4.ª versão aprovada em dezembro de 2013 Instruções de utilização para o doente – 2.ª versão aprovada em dezembro de 2013 Instruções de utilização para o doente (brochura) – 2.ª versão aprovada em dezembro de 2013
Tysabri (natalizumab)	***Information for prescribing physicians*** Informação para o médico – 8.ª versão aprovada em abril de 2014 ***Information for patients*** Formulário de início de tratamento – 7.ª versão aprovada em abril de 2014 Formulário de continuação de tratamento – 7.ª versão aprovada em abril de 2014

Educational Materials published on the Infarmed website
(January to May 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Valdoxan (agomelatine)	***Information for prescribing physicians*** Informação de segurança para os profissionais de saúde – 4.ª versão aprovada em janeiro de 2014 Esquema para a monitorização da função hepática no tratamento com Valdoxan
Velcade (bortezomib)	***Information for health professionals*** Posologia e duração dos ciclos de tratamento para regimes de indução para transplante de Velcade – 1.ª versão aprovada em fevereiro de 2014
Xalkori (crizotinib)	***Information for health professionals*** Material educacional para o profissional de saúde – 2.ª versão aprovada em outubro de 2013 ***Information for patients*** Material educacional para o doente – 2.ª versão aprovada em outubro de 2013
Xeomin (botulinum toxin A)	***Information for prescribing physicians*** Informação importante de segurança destinada a médicos – 3.ª versão aprovada em fevereiro de 2014 ***Information for patients*** Informação importante de segurança para o doente – 3.ª versão aprovada em fevereiro de 2014
Yervoy (ipilimumab)	***Information for patients*** Guia para o doente – 2.ª versão aprovada em dezembro de 2013 Cartão de alerta para o doente – 2.ª versão aprovada em dezembro de 2013 ***Information for health professionals*** Guia para o médico – 2.ª versão aprovada em dezembro de 2013

Compiled by Magda Pedro

Comunications to Healthcare Professionals
(March to May 2014)

Medicinal product (DCI)	Click on the topic for details (in Portuguese)
Cosopt (timolol + dorzolamide)	Potential risk of eye injury due to change in pipette
Efient (prasugrel)	Inscreased risk of serious haemorrhage.
Granocyte (lenograstim)	Risk of systemic capillary leak syndrome in patients with cancer and in healthy donors
Protelos/Osseor (strontium ranelate)	New indication restriction and recommendations for monitoring of use
Soro Fisiológico Basi (sodium chloride) e Glucose 5% com Cloreto de Sódio 0,9% Basi)	Inadequate labelling

Compiled by Catarina Costa

Online reporting of adverse drug reactions by health professionals and patients

Portal RAM for ADR reporting.
Online forms for both
health professionals and patients.

How can I report an adverse reaction?

- **ADR Portal (Portal RAM):**
http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
- **Report Card online printout link:**
http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/ficha_notificacao_profsaude.pdf
- **OR:**

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Site: http://aibili.pt/ufc_about.php

What do they stand for?

ADR Adverse Drug Reaction

EMA (European Medicines Agency)

MA Marketing Authorisation

PIL Patient Information Leaflet

PRAC Pharmacovigilance Risk Assessment Committee

SmPC Summary of the Product's Characteristics

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