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From the Editor

Variety in this quarter with one common theme: the relevance of considering risk factors and monitoring therapy as adverse reaction risk minimization tools in clinical practice.

From valproate in pregnant women with epilepsy to the risk of skin lesions caused by topical chlorhexidine in premature newborns, this issue will also walk you through other diverse topics such as the "return" of the polymixins for refractory infections and how to use them safely, monoclonal antibodies and renal and coagulation risks, special caution with the antianginal drug ivabradine, cardiovascular risk and testosterone replacement therapy, antiandrogens and potential for QT interval prolongation.

You can find links to the latest educational materials and communications to health professionals in their corresponding sections. Additionally, we suggest you bookmark the Infarmed Safety Alerts page:

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

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Valproate and Valproic Acid
Safety in pregnant women and in women of childbearing age in general

Quick Read

Remember that the use of valproate / valproic acid is restricted in pregnant women and in women of childbearing age in general on account of the attending risk of malformations and developmental problems in children exposed during gestation.

Medicinal products containing valproate and valproic acid, of which several are marketed in Portugal, are used in the treatment of epilepsy and bipolar disorder.

Information in their **SmPCs** reflects the fact that the use of antiepileptic agents during pregnancy increases the risk of congenital malformations in the offspring. **PRAC** has concluded a safety review following the publication of **studies**[1-9] suggesting that in certain children the developmental problems could be prolonged in time.

Treatment of epilepsy or of bipolar disease

- **These medicines should only be prescribed when other therapies are not effective or tolerated, and treatment should be supervised by an experienced physician.**
- Female patients of childbearing age should be alerted to the risks associated with using these medicines during pregnancy. They should be advised to use effective contraception during treatment.
- Alternative therapy should be considered in women who become pregnant or who are planning to become pregnant.
- Therapy should be periodically reviewed in girls nearing puberty.

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Valproate and Valproic Acid
Safety in pregnant women and in women of childbearing age in general

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Migraine prophylaxis

- **The use of these medicines is contraindicated in female patients of childbearing age who are not using effective contraception or who are pregnant.**
- Patients of childbearing age should be made aware of the importance of staying on effective contraception throughout therapy, as well as of the risks associated with using these medicines while pregnant. Pregnancy should be excluded before therapy is started.
- Alternative therapy should be considered in women who become pregnant or who are planning to become pregnant.

Leonor Chambel

[1] *Meador K et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81(1):1-13.*

[2] *Meador KJ et al. Antiepileptic drug use in women of childbearing age. Epilepsy Behav 2009;15(3):339-43*

[3] *Bromley RL et al. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology 2008;71(23):1923-4.*

[4] *Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011 July;96(7):643-7.*

[5] *Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav 2008 Jul;13(1):229-36.*

[6] *Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013 Apr 24;309(16):1696-1703.*

[7] *Cohen MJ et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. Epilepsy Behav 2013;29(2):308-15*

[8] *Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. Epilepsy Behav 2011 Oct;22(2):240-6.*

[9] *Meador KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12(3):244-52.*

Chlorhexidine
Risk of chemical injury in newborns

Quick Read

There is a risk of serious chemical burns from using chlorhexidine solutions in premature babies, especially in those born before the 32nd week of gestation and during their first two weeks of life.

PRAC has reviewed 44 cases from various sources of newborns who sustained chemical burns on the application of chlorhexidine solutions. Seriousness ranged from intense skin redness to chemical injury/burn, skin grazing, skin rupture. Most neonatal intensive care units seem to use chlorhexidine solutions mainly in preparation for a central vascular access, umbilical catheterization and peripheral venous access.[1] In general, there is **considerable variation** in the type and concentration of the solutions used, as well as in use limitations to do with weight at birth, or gestational or chronological age.

Based on the data analysed, it seems that there is an increased risk of skin toxicity in newborns with **less than 32 weeks of gestational age** and whenever chlorhexidine is applied **within the first two weeks of life** for disinfecting the skin before invasive procedures.

From a physiological point of view, very and extremely premature babies are at greater risk, since their skin barrier function is not as well developed as in older children. Although data point to a higher frequency of chemical burns with the use of alcohol-based solutions and of the more concentrated chlorhexidine solutions, no conclusion can be drawn regarding the relative safety of different types of chlorhexidine solutions, due to lack of exposure data.

It is necessary that professionals be made aware of the relevance of **changing all wet or soaked materials or surgical fields** before proceeding with catheter insertion, and of avoiding any prolonged contact or exposure of the skin to chlorhexidine. Though evidence is not abundant, data from the literature do underline a greater risk of adverse skin reactions in newborns and older children when chlorhexidine-impregnated plasters are used, as compared to using chlorhexidine before the procedure only. Further studies are needed so that ideal protocols for antiseptic use in term and preterm babies can be established.

Based on the available data, **PRAC** has recommended that the **MA** holders of all chlorhexidine-containing solutions change the wording in their **SmPCs**, Information Leaflets and packaging labels. The Portuguese version of the texts to be implemented is available at Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Key messages:

- There is a risk of serious chemical burns when either alcohol or water-based chlorhexidine solutions are used in premature babies.
- Risk seems to be greater in premature babies (especially those born before the 32nd week of gestation) and in the first two weeks of life.
- The smallest quantities necessary of chlorhexidine solution should be used, and the solutions should not be left to accumulate in skin folds or under the patient, nor spilt on to the surgical field or any other material that may be in direct contact with the patient.
- Patients should be closely monitored so that any collateral skin effects may be detected and acted upon at an initial stagel.

Márcia Silva

[1] *Loveday HP et al. epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England, Journal of Hospital Infection 86S1 (2014) S1–S70.*

Polymyxins
Recommendations for use

Quick Read
Polymyxins have been coming back to clinical practice in cases where scant therapeutic choices are left. Specific measures of caution should be exerted when using them.

Polymyxins make up a group of antibiotics which have been available since the 1960s but whose use decreased when other antibacterial agents with fewer collateral effects appeared. Partly due to its limited use, colistimethate sodium has remained active against bacteria which are resistant to a range of common antimicrobials. This has recently led to its use in patients with few therapeutic alternatives. However, clinical practice has highlighted the fact that information in **SmPCs** and patient leaflets needs to be updated, namely in what concerns dosing and pharmacokinetics. For this reason, the European Commission has asked **EMA** to assess the available pharmacokinetic, efficacy and safety data of these medicinal products. The analysis included medicines for systemic use given only by injection, inhalation (containing colistimethate sodium which is converted by the body into colistin) and *per os* (containing mainly colistin and acting on the gastrointestinal tract).

In Portugal two products containing colistimethate sodium are used in the hospital setting: *Colistina Generis* and *Colixin*.

EMA and Infarmed recommend the following to health professionals:

- Parenteral administration of colistimethate sodium should be reserved for the treatment of serious **Gram-negative** bacterial infections in **patients with limited therapeutic options**. Whenever possible, an association with another antimicrobial should be considered.
- Dosing should be expressed in International Units (**IU**) of colistimethate sodium and the **SmPCs** and **PILs** should contain the following conversion table:

Colistimethate sodium (UI)	Colistimethate sodium (mg)	Colistin base activity (CBA) (mg)*
12,500	1	0.4
150,000	12	5
1,000,000	80	34
4,500,000	360	150
9,000,000	720	300

*Based on an active ingredient nominal strength of 12,500 U.I./mg or 0.424 mg CBA/mg: the units IU and mg CBA are expressions of strength and only approximately relate to the mass of active ingredient.

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Polymyxins
Recommendations for use

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- The **daily recommended dose** for adults is 9 million IU divided in 2 or 3 slow intravenous doses; in critical patients a loading dose of 9 million IU may be given.
- In patients with **renal insufficiency** the dose should be reduced according to creatinine clearance.
- In **children** the recommended dose is 75,000 to 150,000 IU/kg/day, divided in 3 doses.
- IV colistimethate sodium does not significantly cross the blood-brain barrier. For **intraventricular or intrathecal** administration the maximum recommended dose in adults is 125,000 IU.
- Colistimethate sodium can be administered via inhalation in the treatment of chronic pulmonary infections by **Pseudomonas aeruginosa in adults and children with cystic fibrosis**. The recommended dose in adults is 1 to 2 million IU (two to three times a day) and in children it is 0.5 to 1 million IU (twice a day), to be adjusted according to severity and response to treatment.
- Caution should be exercised when using IV colistimethate sodium and potentially **nephrotoxic or neurotoxic** medicines concomitantly.

These recommendations are based in reviews of available clinical, pharmacological and pharmacokinetic data, although significant gaps still exist in what concerns pharmacokinetics in special populations, such as children and patients with renal impairment. Ongoing research may come to provide us with further useful pharmacodynamics and pharmacokinetics data. In the meantime, **SmPCs** and **PILs** are to be updated across the EU in order to include the already available information.

Sílvia Duarte

Imatinib
Renal insufficiency associated with prolonged use

Quick Read
Long term treatment with imatinib may compromise renal function.

Imatinib is indicated for the treatment of patients diagnosed de novo with Philadelphia (bcr-abl) chromosome positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplant is not a first-line treatment option, as well as for other patients, such as those with Ph+ CML in chronic phase after therapeutic failure with alfa-interferon, or in accelerated phase, or in blastic crisis.

Following an article published in the Annals of Oncology[1], a potential safety issue has been raised to do with decreased estimated glomerular filtration rate (eGFR).

PRAC has noted that data show that acute renal failure is a possible adverse reaction. However, there was insufficient evidence on the effect on kidney function of prolonged treatment and the occurrence of chronic progressive renal failure in these patients. An analysis of clinical trials revealed a consistent trend towards increasing serum creatinine levels and decreasing glomerular filtration rate.[2]

Post-marketing data have also identified cases suggesting decreased/abnormal eGFR or creatinine clearance. Most patients had other comorbidities or were concomitantly using other medicines that may affect renal function.

Although it has to be taken into account that ageing is also associated with declining renal function, **PRAC** has concluded, based on available evidence, that long-term treatment with imatinib may compromise kidney function. An update of information pertaining to the medicinal products containing imatinib has therefore been deemed necessary to reflect the above concerns.

The Portuguese translation of the texts to be included in the **SmPC** and **PIL**s will be available at: Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Margarida Guimarães

[1] Marcolino MS et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. Ann Oncol. 2011 Sep;22(9):2073-9. doi: 10.1093/annonc/mdq715. Epub 2011 Feb 10.

[2] Cortes JE et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronicmyeloid leukemia:Results from the BELA trial. J Clin Oncol 2012;30:3486–3492.

Ponatinib
Assessment prior to treatment and monitoring

Quick Read
The benefit-risk relation of ponatinib is still favourable for the established indications and as long as measures are put in place to minimize the occurrence of arterial or venous obstruction by blood clots.

Iclusig (ponatinib) is an antineoplastic agent which belongs to the class of tyrosine-kinase inhibitors. It is used in the treatment of **chronic myeloid leukaemia** and **Philadelphia chromosome positive acute lymphoblastic leukaemia**, in patients who cannot tolerate dasatinib and/or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

EMA has conducted a benefit-risk assessment from which the need emerged to reinforce measures to **minimize** the occurrence of **arterial or venous obstruction caused by blood clots**.

EMA and Infarmed recommend the following to health professionals:

- The benefit-risk ratio is still favourable for all the approved indications, and the **initial dose** should still be 45 mg once daily.
- The patient's **cardiovascular function** should be assessed before therapy is started and frequently monitored throughout the treatment.
- Treatment should be stopped in patients who show no response after **three months**.
- In case there is any evidence of toxicity, **changes in dose or discontinuation** should be considered.
- Whenever the **dose is reduced**, the doctor should monitor the therapeutic response. Although data seem to indicate that risk is dose related, they are not sufficiently robust to allow for a formal recommendation for the use of lower doses, since their efficacy may be reduced.

The safety and efficacy data regarding the use of lower doses followed by greater cytogenetic response have been included in the **SmPC**. Additionally, educational materials will be made available to stress major risks and recommended minimization measures.

The **MA** holder, on **EMA's** indication, is to perform a **study** in patients with chronic myeloid leukaemia to determine the optimal initial dose and to further characterize safety and efficacy aspects associated with dose reduction. **EMA** will assess the results as soon as they become available.

Sílvia Duarte

Ivabradine
SIGNIFY and use restrictions

Quick Read

In order to reduce cardiac problems associated with the antianginal ivabradine, specific indication selection and treatment monitoring measures should be applied. Concomitant use with verapamil or diltiazem is contraindicated.

Ivabradine is an antianginal drug used for the symptomatic treatment of stable chronic angina pectoris in adults with coronary disease in sinus rhythm, as well as for chronic cardiac failure. In Portugal only *Procoralan* is marketed.

In April 2014, **EMA** performed a safety review following the publication of the preliminary results of the SIGNIFY study on whether ivabradine in coronary patients reduces the rate of cardiovascular events when compared to placebo. In November 2014, in order to reduce cardiac problems and to keep a favourable benefit-risk ratio for ivabradine, the following restrictions of use were adopted:

- Ivabradine shows no benefit for heart patients without clinical cardiac failure. It is only beneficial for the symptomatic treatment of stable chronic angina pectoris in patients who cannot take beta-blockers, or in combination with beta-blockers when the latter do not fully keep the condition under control.
- **Concomitant use of ivabradine and verapamil or diltiazem is contraindicated.**

- Symptomatic treatment of patients with stable chronic angina pectoris should only be started if **the patient's resting heart rate is equal to or higher than 70** beats per minute (bpm).
- The **initial dose** should not exceed **5 mg twice daily**, and the maintenance dose should not be higher than 7.5 mg twice daily.
- Treatment should be stopped if, after **3 months**, there is no improvement in anginal symptoms. Discontinuation should also be considered should there be no significant improvement in symptoms and a clinically relevant reduction of the resting heart rate after three months.
- **Before treatment is started or whenever changing dose**, in order to determine the heart rate, ambulatory 24-hr monitoring, ECG and systematic heart rhythm measurements should be considered.
- The risk of **atrial fibrillation** is increased in patients treated with ivabradine, for which they should be regularly monitored. Should atrial fibrillation supervene during treatment its maintenance should be pondered.
- If, during treatment, the resting heart rate becomes lower than 50 bpm, or if the patient shows other symptoms suggestive of bradycardia, the dose should be reduced (the lowest dose being 2.5 mg twice daily). Treatment should be discontinued in case the heart rate stays below 50 bpm or symptoms of bradycardia persist despite the dose reduction.

Leonor Chambel

Testosterone
Safety recommendations

Quick Read
Special consideration should be given to cardiovascular risk and events when starting and monitoring testosterone replacement therapy.

Testosterone is used in men who do not produce sufficient quantities of this hormone (hypogonadism). Following a study that suggested that testosterone use increased the risk of myocardial infarction in men older than 65 years, as well as in younger men with preexisting cardiac disease,[1] **EMA** conducted a safety review which concluded that there is no consistent evidence on increased risk.

EMA recommendations to be reflected in the **SmPCs** and **PILs** are:

- Testosterone replacement therapy should only be used in men with **clinically proven hypogonadism**.
- During treatment, testosterone levels, haemoglobin, haematocrit, liver function and the lipid profile should be **regularly monitored**.
- Testosterone should be used with **caution in hypertensive patients**, since it may raise blood pressure.
- Treatment should be **promptly discontinued** in men with severe cardiac, hepatic or renal failure, or with ischaemic heart disease, on account of the risk of serious complications, such as oedema associated or not to congestive heart failure.
- Safety and efficacy data in patients **over 65 years of age** are limited; testosterone given to increase hormone levels in **healthy men** of this age range is therefore **not approved**.

Ana Sofia Martins

[1] *Finkle et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014 Jan 29;9(1):e85805.*

Antiandrogens
Prolonged QT from long-term use?

Quick Read

The target population for antiandrogen therapy is usually elderly and with greater likelihood of preexisting heart disease or other cardiovascular risk factors. Since QT interval prolongation is itself a risk factor for ventricular tachyarrhythmia, its potential occurrence with antiandrogens is of relevance for the target patient population.

In April 2014, **PRAC** discussed a labelling change for triptorelin to include a warning on the risk of QT interval prolongation from long-term use. This proposal had been made by the **MA** holder and was based on the fact that antiandrogens, by indirectly diminishing the levels of testosterone to castration-like levels, affect QT refractory times; an effect across the whole range of this class of medicines was also suggested.

Some of the medicinal products of this class already contained information regarding QT prolongation in their **SmPCs**, and available data on cardiovascular class effects had already been reviewed earlier in 2012. Therefore, and in spite of the limited evidence presented, **PRAC** decided that this potential safety issue ("signal") should be further explored. A search for cases of QT interval prolongation, *torsades de pointes* and ventricular fibrillation was undertaken in the European Eudravigilance database, and the available literature reviewed.

Detecting safety issues relating to silent QT prolongation is a challenge, in that it is often only diagnosed when serious events occur, such as ventricular fibrillation or sudden death. Few cases were found in the Eudravigilance database and no clear potential association was found with antiandrogens. Some evidence emerged from the literature that there may be QT prolongation with antiandrogen treatment, but its clinical significance was limited and only a small increase was found, of between 30 and 60 ms.[1-3]

Given that QT interval prolongation is a risk factor for ventricular tachyarrhythmia and that the target population for antiandrogen therapy is usually elderly and with greater likelihood of preexisting heart disease or other cardiovascular risk factors, QT prolongation even if moderate may be of great relevance for this population.

Information in the SmPCs and PILs will thus be updated across all the medicines of this class: **buserelin, leuprorelin, goserelin, triptorelin, histrelin, abarelix, dagarelix, abiraterone, flutamide, nilutamide, bicalutamide, enzalutamide**.

The Portuguese version of the texts to be implemented can be found at Recomendações do PRAC decorrentes de avaliação de sinais de segurança

Sílvia Duarte

[1] *Garnick MB et al. The effect of hormonal therapy for prostate cancer on the electrocardiographic QT interval: phase 3 results following treatment with leuprolide and goserelin, alone or with bicalutamide, and the GnRH antagonist abarelix Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 4578.*

[2] *Smith MR et al. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. J Urol. 2010 Dec;184(6):2313-9.*

[3] *Sağlam H et al. Changes in Electrocardiogram Findings during Treatment with Gonadotropin-Releasing Hormone Agonist and Surgical Castration for Prostate Carcinoma Open Journal of Urology Vol.2 No.3A, October 2012.*

Educational Materials published on the Infarmed website
(September to November 2014)

Medicinal Product (DCI)	Click on topic for details (in Portuguese)
Artiss (aprotinin, human fibrinogen, human thrombin and calcium chloride)	***Information for healthcare professionals*** Carta de rosto Guia de referência Guia de referência rápida do EASYSPRAY (para cirurgia por via aberta) Listas de verificação da pressão e distância corretas para aplicação – 1.ª versão aprovada em agosto de 2014 For surgeons, staff in charge of operating theatres, and all operating theatre nurses using Tisseel, Tisseellyo and/or Artiss with pressure regulating devices. See also specific educational materials for Tisseel and Tisseellyo.
Binocrit (epoetin alfa)	***Information for physicians*** Informação de segurança – 2.ª versão aprovada em julho de 2014 For all healthcare or dialysis units procuring the product.
Entyvio (vedolizumab)	***Information for physicians*** Brochura – 1.ª versão aprovada em agosto de 2014 For gastroenterologists and internal medicine physicians.
Hemangiol (propranolol)	***Information for physicians*** Instruções de utilização e minimização de risco – 1ª versão aprovada em setembro de 2014 Destacável For physicians expected to prescribe Hemangiol, namely paediatricians and dermatologists. ***Information for caregivers*** Guia – 1.ª versão aprovada em setembro de 2014 To be handed out to the caregiver by the doctor on prescribing the medicine.
Humira (adalimumab)	***Information for patients / caregivers*** Cartão de segurança – 1.ª versão aprovada em agosto de 2014 Guia de administração – 1.ª versão aprovada em agosto de 2014

Educational Materials published on the Infarmed website
(September to November 2014)

Medicinal Product (DCI)	Click on topic for details (in Portuguese)
Incivo (telaprevir)	***Information for healthcare professionals*** Informação – 3.ª versão aprovada em agosto de 2014 For all healthcare professionals dealing with patients with hepatitis C infection, namely infectious disease specialists, gastroenterologists and internists.
Increlex (mecasermin)	***Information for patients*** Informação – 3.ª versão aprovada em novembro de 2014 ***Information for physicians*** Informação – 3.ª versão aprovada em novembro de 2014 For paediatric endocrinologists and paediatricians who provide endocrinological services at major National Health Service hospitals.
Leflunomida Medac (leflunomide)	***Information for physicians*** Folheto Informativo – 2.ª versão aprovada em setembro de 2014
Pradaxa (dabigatran)	***Information for physicians*** Guia de prescrição para o tratamento da trombose venosa profunda (TVP) e da embolia pulmonar (EP), e prevenção da TVP e da EP recorrente em adultos – 1.ª versão aprovada em setembro de 2014 Guia de prescrição para a prevenção do AVC em doentes com fibrilhação auricular – 7.ª versão aprovada em setembro de 2014 Guia de prescrição para a prevenção primária de fenómenos tromboembólicos venosos – 7.ª versão aprovada em setembro de 2014 For family doctors, cardiologists, internists, neurologists, haematologists, pathologists, gastroenterologists, orthopaedic surgeons, immunohaemotherapists, anaesthetists, vascular surgeons, and general surgeons.
Protelos/Osseor (strontium ranelate)	***Information for physicians*** Guia de prescrição – 1.ª versão aprovada em setembro de 2014 Lista de verificação – 1.ª versão aprovada em setembro de 2014 For rheumatologists, internists, family doctors, gynaecologists, orthopaedic surgeons, and rehabilitation medicine specialists. ***Information for patients*** Cartão informativo – 1.ª versão aprovada em setembro de 2014

Educational Materials published on the Infarmed website
(September to November 2014)

Medicinal Product (DCI)	Click on topic for details (in Portuguese)
Qutenza (capsaicin)	***Information for physicians*** Informação de segurança sobre manuseamento e eliminação – 3.ª versão aprovada em setembro de 2014
RoActemra (tocilizumab)	***Information for healthcare professionals*** Brochura – 5.ª versão aprovada em junho de 2014 For physicians, nurses and pharmacists. ***Information for patients*** Brochura – 1.ª versão aprovada em junho de 2014 Cartão de alerta – 1.ª versão aprovada em setembro de 2014
Tisseel/Tisseellyo (human fibrinogen, factor XIII, human thrombin, aprotinin and calcium chloride)	***Information for healthcare professionals*** Carta de rosto Guia de referência rápida do DUPLOSPRAY (procedimentos laparoscópicos) Guia de referência rápida do EASYSPRAY (para cirurgia por via aberta) Listas de verificação da pressão e distância corretas para aplicação – 1.ª versão aprovada em agosto de 2014 For surgeons, staff in charge of operating theatres, and all operating theatre nurses using Tisseel, Tisseellyo and/or Artiss with pressure regulating devices. See also specific educational materials for Artiss.
Vfend (voriconazole)	***Information for physicians*** Carta – 1.ª versão aprovada em agosto de 2014 Lista de verificação – 1.ª versão aprovada em agosto de 2014 Brochura – 1.ª versão aprovada em agosto de 2014 For haematology, infectious diseases, dermatology and STDs, and oncology specialists. ***Information for patients*** Cartão de alerta – 1.ª versão aprovada em agosto de 2014

Compiled by Magda Pedro

Communications to Healthcare Professionals (September to November 2014)

Medicinal Product (DCI)	Click on topic for details (in Portuguese)
Avonex, Betaferon, Extavia, Pegintron e Rebif (interferon beta)	Risk of thrombotic microangiopathy and nephrotic syndrome
Lentocilin (penicillin)	Temporarily out of stock
Periolimel/olimel (aminoacids + electrolytes + glucose + lipids)	Correct preparation and administration User guide
Prolia (denosumab)	Risk of jaw osteonecrosis and hypocalcaemia
SonoVue (sulphur hexafluoride)	Contraindications, warnings and caution in patients with cardiovascular instability
Stelara (ustecinumab)	Risk of exfoliative dermatitis and skin exfoliation
Vibativ (telavancin)	Nephrotoxicity, QT interval prolongation, reproductive toxicity
Xofigo (radium dichloride)	Temporarily out of stock Special temporary preparation instructions

Compiled by Sílvia Duarte

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
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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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