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From the Editor

Risk Management Plans, Periodic Safety Update Reports and Portugal's contribution to work sharing in medicinal product safety reviews in Europe: three visible facets of the intense and continuing safety assessment and monitoring activities that go on at a European and national level.

In this issue we have the usual sections on the most recent educational materials and communications to healthcare professionals, as well as a pot pourri of articles on other specific topics: proton pump inhibitors and cutaneous lupus erythematosus, sofosbuvir and risk-benefit balance, donepezil and adverse muscle reactions, adrenaline auto-injectors and the need to educate patients and care-givers.

Current and previous safety alerts issued by Infarmed can be found at:

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

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Director:
Alexandra Pego

Editor:
Rui Pombal

Assistant Editor:
Leonor Nogueira Guerra

Contributors:
Ana Sofia Martins
Cristina Mousinho
Fátima Bragança
Fátima Hergy
Leonor Chambel
Leonor Nogueira Guerra
Magda Pedro
Márcia Silva
Margarida Guimarães
Pedro Marques Silva
Sílvia Duarte

Publishing Assistant:
Inocência Pinto

Advisory Board:
Conselho Diretivo do INFARMED, I.P.
Comissão de Avaliação de Medicamentos

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

Parque de Saúde de Lisboa
Av. do Brasil, N.º 53, 1749-004 Lisboa

Phone:
+351 217 987 100

E-mail:
infarmed@infarmed.pt

Design and production:
Letras & Sinais
Comunicação e Imagem, Lda.

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Risk Management Plans

Quick Read

To find a list and further information on safety concerns raised by risk management plans Europe-wide click here: http://www.hma.eu/464.html

It is widely recognized that data on the safety of a medicinal product at the time its **MA** is given is relatively limited. Medicines have various possible types of risk that can be minimized thanks to the implementation of risk management systems.

The main goal of risk management is to ensure that the product's benefits overtake its risks. It is structured into a Risk Management Plan (RMP) containing activities and interventions designed to prevent and minimize risks. In July 2012 it became mandatory to present an RMP for every single new **MA**.

An additional aim of RMPs is to harmonize safety concerns and their corresponding pharmacovigilance / risk minimization activities for the same active ingredient.

Nevertheless, available information on already previously approved RMPs, such as is the case of older reference products, has been deemed scarce. In order to remedy this gap in a viable way the publication of a list has been agreed on which contains the safety concerns included in the approved RMPs. This list is organized by medicinal product / active ingredient and the Working Party on Pharmacovigilance Procedures Work Sharing will be in charge of keeping it up to date. You can find it at: http://www.hma.eu/464.html

Margarida Guimarães

Periodic Safety Update Reports:
Conclusions published online

Quick Read

The conclusions from the periodic safety update reports of the medicinal products marketed Europe-wide are now accessible both through specific one-click links and on Infarmed's website.

EMA has recently started to publish the conclusions issued from the **periodic safety update reports (PSURs)** of medicines authorized via national procedure. This aims to facilitate a harmonized implementation of safety measures adopted for all the products containing the same active ingredient across all the European Union member states.

At European Medicines Agency - Outcomes of periodic safety update report single assessments,the following are now available:

- The scientific conclusions and rationale for changes to medicinal product information and the corresponding implementation calendar in all the EU official languages;
- The list of the medicines concerned.

This includes the conclusions stemming from PSUR single assessments involving only products authorized through national procedure, of mutual recognition or decentralized (non-centralized).

As for **centralized procedure** medicines, their assessment conclusions are published under the European Public Assessment Report (EPAR) for each product. The conclusions for medicines authorized through **centralized and non-centralized procedure** are published in the Community register of medicinal products | Public health, European Commission.

The **MA** Holders of the medicines concerned (including generics and those of well-established use) should adopt the measures laid out in the above conclusions, including submission of changes to the terms of their **MA**.

To facilitate the implementation of conclusions from the assessment of all the procedures involving at least one non-centralized **MA** (be it national, mutual recognition or decentralized), **Infarmed** regularly **publishes** the summaries of the safety update reports at Relatórios Periódicos de Segurança – conclusões da avaliação única.

MA holders are legally bound to ensure that their products' data is kept up to date taking into account the most recent scientific knowledge and the recommendations published on the **EMA** website, effectively the European medicines portal.

Sílvia Duarte

Portugal

One of the most active EU member states in pharmacovigilance work sharing

Quick Read

Portugal is among the EU member States with the most intense medicinal product safety monitoring activity within the scope of EU-wide work sharing.

Within the scope of its active membership of **EMA**'s Pharmacovigilance Risk Assessment Committee (**PRAC**), Infarmed (the Portuguese medicines agency) is the third most active **pharmacovigilance Rapporteur** within the European system. A rapporteur is a country in charge of monitoring and assessing medicinal products at a European level.

The **PRAC** is a scientific committee made up of members designated by the EU member States, experts designated by the European Commission and representatives of healthcare professionals and patient associations. It is in charge of assessing aspects of human use medicinal product risk management, including detection, assessment, minimization and communication regarding the risk of occurrence of adverse reactions.

Medicinal product assessment as a pharmacovigilance Rapporteur is to do with medicines authorized through **centralized procedures** approved by the European Commission. Infarmed's participation in the European assessment system has been constant, growing and significant since 2012, the year when the most recent pharmacovigilance legislation came into force and **PRAC** was created, in consonance with the objectives defined by the national Authority.

In 2012 Portugal was not yet in charge of any new procedure, but by 2013 it had become the 10th member State in charge of the most procedures (three). From 2014 to 2015, with eight procedures, Portugal became the third member State with the most procedures. At the top of the list are the Netherlands (thirteen procedures) and the United Kingdom (nine) (Fig. 1).

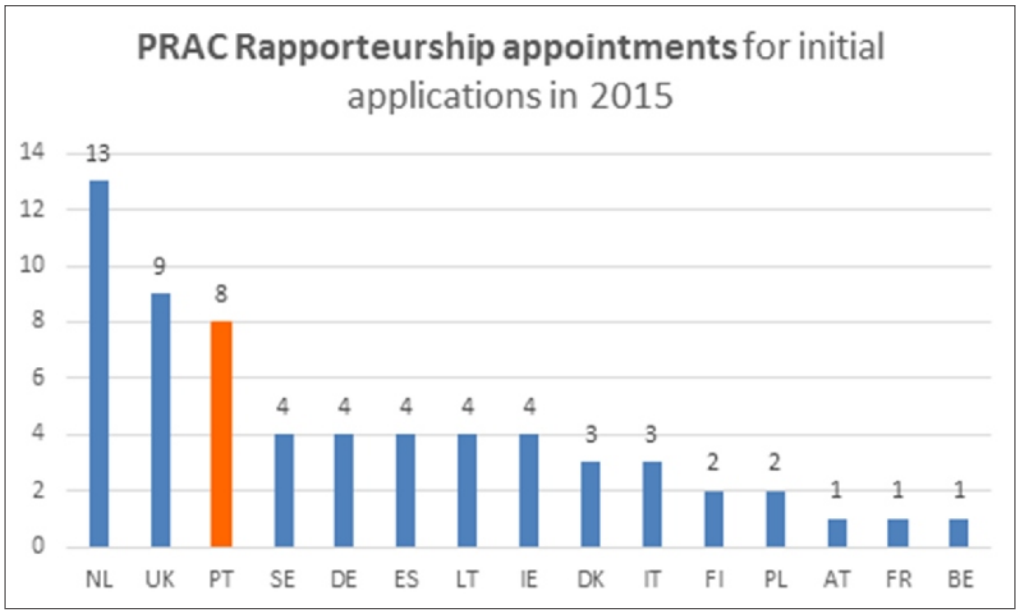

Figure 1. Centralized procedures for approval of new medicinal products – distribution of Rapporteur countries (in **EMA** website).

Portugal
One of the most active EU member states in pharmacovigilance work sharing

Infarmed is moreover the second national Authority within the EU and whilst a **PRAC** member with the most Rapporteurships in arbitration procedures. These are safety reviews undertaken at a European level aiming to reassess the benefit/risk ratio of a medicinal product or of a class of medicines / active ingredients. Since 2012, Infarmed has been the Rapporteur for three safety arbitration procedures, as many as the Spanish or the Swedish Authorities. The German, Dutch and UK Authorities have so far had the Rapporteurship for 5 procedures each (Fig. 2).

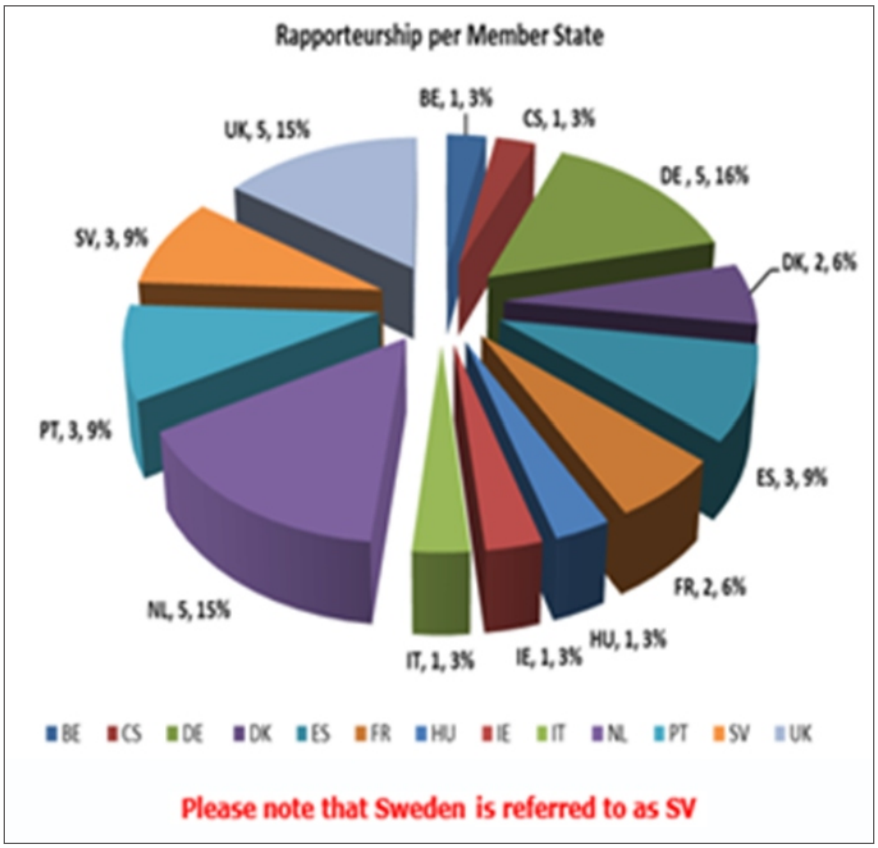

Figure 2. Arbitration procedures – distribution of Rapporteur countries in 2015 (in **EMA** website).

Portugal's current position is an opportunity to further strengthen Infarmed's technical and scientific competencies, as well as a recognition of the quality of its assessment work within the EU. Portugal has shown a proactive attitude in leading and following up on several European safety monitoring procedures. This growing intervention capability underscores the country's relevance within the system and Infarmed's position amongst the member State Authorities.

Margarida Guimarães

Proton Pump Inhibitors:
Risk of subacute cutaneous lupus erythematosus

Quick Read

Subacute cutaneous lupus erythematosus: think of including PPIs in the differential diagnosis.

In October 2014, during routine pharmacovigilance activities, **EMA** raised a safety signal based on literature case studies1-18 and the EudraVigilance database, which potentially associated pantoprazole with the appearance of subacute cutaneous lupus erythematosus (SCLE). More recent evidence suggested that drug-induced SCLE could be associated with any proton pump inhibitor (PPI).

The **PRAC** decided to request from the **MA** Holder of the reference medicine pantoprazole a cumulative review of the cases of SCLE associated with the drug, at the same time emphasizing the possibility of cross-reactivity among the various PPIs. **PRAC** later concluded that, in light of the analyzed data pertaining to the medicines in the PPI class, SCLE could be induced by such medicines. It therefore recommended that **MA** Holders of medicinal products containing dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole, submit changes to the **SmPC** texts (sections 4.4 and 4.5) as well as to the **PIL**s (sections 2 and 4), in order to include SCLE.

The Portuguese language versions of the texts to be implemented can be found at: http://www.ema.europa.eu/docs/pt_PT/document_library/Other/2015/08/WC500191719.pdf

Leonor Chambel

[1] *Sandholdt LH et al. Proton pump inhibitor-induced subacute cutaneous lupus erythematosus. Br J Dermatol. 2014 Feb;170(2):342-51. (EV, case 1 and 2)*

[2] *Cookson H et al. Proton pump inhibitors and subacute cutaneous lupus erythematosus: an under-recognized phenomenon? Br J Dermatol. 2014 Feb;170(2):235.*

[3] *Almebayadh M et al. Subacute cutaneous lupus erythematosus induced and exacerbated by proton pump inhibitors. Dermatology. 2013;226(2):119-23 (EV, case 3)*

[4] *Reich A et al. Subacute cutaneous lupus erythematosus due to proton pump inhibitor intake: case report and literature review. Arch Med Sci. 2012 Sep 8;8(4):743-7*

[5] *Grönhagen CM et al. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case-control study of 234 patients in Sweden. Br J Dermatol. 2012 Aug;167(2):296-305.*

[6] *Wee JS, et al. A difficult diagnosis: drug-induced subacute cutaneous lupus erythematosus (SCLE) triggered by omeprazole in a patient with pre-existing idiopathic SCLE. Clin Exp Dermatol. 2012 Jun;37(4):445-6.*

[7] *Alcántara-González J et al. Esomeprazole-induced subacute cutaneous lupus erythematosus. Actas Dermosifiliogr. 2011 Oct;102(8):638-40.*

[8] *Lowe G et al. A systematic review of drug-induced subacute cutaneous lupus erythematosus. Br J Dermatol. 2011 Mar;164(3):465-72.*

[9] *McCourt C et al. Anti-Ro and anti-La antibody positive subacute cutaneous lupus erythematosus (SCLE) induced by lansoprazole. Eur J Dermatol. 2010 Nov-Dec;20(6):860-1.*

[10] *Toms-Whittle LM, et al. Drug-induced subacute cutaneous lupus erythematosus associated with omeprazole. Clin Exp Dermatol. 2011 Apr;36(3):281-3.*

[11] *Mankia SK, et al. Omeprazole-induced subacute cutaneous lupus erythematosus. Clin Exp Dermatol. 2010 Apr;35(3)*

[12] *Panting KJ, et al. Lansoprazole-induced subacute cutaneous lupus erythematosus. Clin Exp Dermatol. 2009 Aug;34(6):733-4.*

[13] *Dam C, et al. Subacute cutaneous lupus erythematosus induced or exacerbated by proton pump inhibitors. Acta Derm Venereol. 2008;88(1):87-9. (EV, cases 4 and 5)*

[14] *Bracke A, et al. Lansoprazole-induced subacute cutaneous lupus erythematosus: two cases. Acta Derm Venereol. 2005;85(4):353-4*

[15] *Zandman-Goddard G, Solomon M, Rosman Z et al. Environment and lupus-related diseases. Lupus 2012; 21:241–50*

[16] *http://emedicine.medscape.com/article/1065657-overview#a0101*

[17] *Marzano AV, Vezzoli P, Crosti C. Drug-induced lupus: an update on its dermatologic aspects. Lupus. 2009 Oct;18(11):935-40*

[18] *Correia O, et al. Possible phototoxicity with subsequent progression to discoid lupus following pantoprazole administration. Clin Exp Dermatol. 2001 Jul;26(5):455-6. (EV, case 6).*

Sofosbuvir:
Second safety assessment concluded

Quick Read

The benefit-risk ratio of Sovaldi (sofosbuvir) remains favourable. See also Boletim no. 2, 2015.

It is estimated that about 150 to 160 million people are chronically infected with the hepatitis C virus (HCV), of which nine million in Europe.[1,2] Most HCV infected patients progress to chronicity, which may lead on to liver failure, cirrhosis and hepatocellular carcinoma. HCV is the main indication for liver transplant in most countries and the main cause of hepatocellular carcinoma in Japan and Italy.[3-6]

In February 2015, the Portuguese Ministry of Health decided to cover 100% of the cost of treatment with the medicinal product Sovaldi (sofosbuvir) for chronic hepatitis C in adults. A new national strategy for the treatment of hepatitis C was thus started, which is based on a vertical funding model and on a universal accessibility policy aiming to ensure that every patient registered in the National Health Service receives treatment.

In June 2015 the second European periodic safety update report assessment was finalized. It concluded that the benefits from this medicine continue to outweigh its attending risks.

Márcia Silva

[1] Vietri J et al.The burden of hepatitis C in Europe from the patients' perspective: A survey in 5 countries. BMC Gastroenterol. 2013 Jan 17; 13:16.

[2] Ditah I et al. The changing epidemiology of hepatitis C virus infection in the United States: National health and nutrition examination survey 2001 through 2010. J Hepatol. 2014; Article in Press: http://dx.doi.org/10.1016/j.jhep.2013.11.014.

[3] National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C. Hepatology. 2002; 36(5 Suppl 1): S3-20.

[4] Rodriguez-Luna H et al. Natural history of hepatitis C following liver transplantation. Curr Opin Infect Dis. 2004; 17(4): 363-371.

[5] Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat. 1999; 6(1): 35-47.

[6] Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology. 2002; 62(Suppl 1): 8-17.

Donepezil:
Risk of rhabdomyolysis

Quick Read

There seems to be an increased risk of rhabdomyolysis in patients with Alzheimer's disease being treated with donepezil, especially when therapy is started and dosage is stepped up.

Donepezil is a specific and reversible acetylcholinesterase inhibitor which is indicated in the treatment of mild to moderately severe Alzheimer's dementia.

In January 2015 the Canadian medicines agency issued warnings on a serious risk of rhabdomyolysis and neuroleptic malignant syndrome (NMS) associated with the use of donepezil. NMS has been included in the **SmPC**s of donepezil-containing medicinal products since 2012, but the risk of rhabdomyolysis had not been previously assessed. The seriousness of this effect is variable, from asymptomatic increases in creatine phosphokinase to life threatening cases with great elevations in hepatic enzymes, electrolyte imbalance and acute kidney injury.

Patients with Alzheimer's are mostly elderly, on multiple drugs and with multiple comorbidities. This is a fragile population with a high prevalence of immobility, infection, falls, malnutrition and dehydration – in themselves risk factors for rhabdomyolysis. Furthermore, these patients show loss of muscle strength and compromised motor function, so much so that exertion when carrying on with their daily life activities may also cause rhabdomyolysis.[1]

Once it had analyzed all the available data concerning rhabdomyolysis, **PRAC** considered that, irrespective of the added risk factors of this patient population, one cannot exclude the existence of a causal relation between donepezil and the development of rhabdomyolysis or other less serious muscle adverse reactions, such as weakness and pain.

Consequently, **PRAC** has recommended that the **MA** Holders of medicinal products containing donepezil update section 4.8 of the **SmPC**s and section 4 of the **PIL**s to include rhabdomyolysis as a possible adverse effect. The text should mention that the appearance of symptoms was temporally associated with the beginning of treatment or with increases of dose. The translations into Portuguese of the texts to be implemented are available at the **EMA** website at:

New product information wording: extracts from PRAC recommendations on signals adopted at the 6-9 July 2015 PRAC

Ana Sofia Martins

[1] Kuo YM et al. Elevated abeta42 in skeletal muscle of alzheimer disease patients suggests peripheral alterations of AbetaPP metabolism. Am J Path. 2000; 156(3), 797-805.

Adrenaline:
New educational materials and recommendations

Quick Read

Given the uncertain distribution of adrenaline and consequently of the timing of the beginning of its therapeutic effect, two auto-injectors should be prescribed to each patient. The patients and their caregivers should be trained in the use of the devices.

Following a safety review of adrenaline auto-injectors **EMA** has recommended that several measures be put into place to ensure the correct use of this product by both patients and caregivers (see also Boletim no. 3, 2014).

Adrenaline auto-injectors are used in anaphylactic emergencies. They are to be administered intramuscularly whilst awaiting emergency medical help.

The CHMP analyzed the available data and confirmed that the intramuscular route is the way to obtain the fastest response when treating anaphylaxis. There are factors however, which may affect the quantity of adrenaline given into the muscle tissue, namely needle length, the patient's adipose tissue thickness, the angle the auto-injector is placed and the way it works (spring loaded or not), as well as the strength used to activate the device. The CHMP has therefore concluded that it is of the utmost importance that users be trained on how to correctly administer this medicine.

The **MA** Holders of adrenaline auto-injectors should make clearer educational materials available to ensure more effective use. The educational materials should include training devices, detailed audiovisual materials and a checklist for prescribers.

The **PIL**s and **SmPC**s of these products are to be updated with warnings and cautions, including a recommendation for the prescription of two auto-injectors for each patient. The patients should always carry the devices on them, since auto-administration of a second dose may be necessary pending the arrival of help. Recommendations for relatives and caregivers are also included.

In summary, **EMA** and Infarmed recommend:

- Two auto-injectors should be prescribed to each patient, given the uncertainty regarding the distribution of adrenaline and therefore of the start of its pharmacodynamic response.
- It should be ensured that patients or their caregivers are able to correctly administer the medicine.

Margarida Guimarães

Educational Materials published on the Infarmed website
(June to August 2015)

Medicinal product	Click on the links (in Portuguese)
Betroa (drospirenone + ethinylestradiol)	***Information for physicians*** Lista de verificação para os prescritores – 1.ª versão aprovada em maio de 2015 For family doctors and gynaecologists. ***Information for patients*** Perguntas e respostas sobre Betroa: Informação atualizada para as doentes - 1.ª versão aprovada em maio de 2015 For the doctor to hand out to the patient on prescribing the medicine. Cartão de informação para a doente – 1.ª versão aprovada em maio de 2015 For the pharmacist to hand out to the patient on dispensing the medicine.
Elidel (pimecrolimus)	***Information for physicians*** Perguntas e respostas sobre Elidel – 1.ª versão aprovada em junho de 2015 For dermatologists, allergy specialists and paediatricians.
Eligard (leuprorelin acetate)	***Information for healthcare professionals*** Instruções de preparação para o profissional de saúde – 1.ª versão aprovada em junho de 2015 For healthcare professionals who administer and/or prescribe Eligard, namely nurses and doctors specialized in urology, internal medicine and oncology.
Esbriet (pirfenidone)	***Information for physicians*** Lista para verificação de segurança para o médico – 1.ª versão aprovada em fevereiro de 2015 For pneumologists.
Gilenya (fingolimod)	***nformation for physicians*** Guia e lista de verificação do médico prescritor – 4.ª versão aprovada em abril de 2015 For neurologists. ***Information for patients*** Cartão de informação para o Doente – 4.ª versão aprovada em abril de 2015

Educational Materials published on the Infarmed website
(June to August 2015)

Medicinal product	Click on the links (in Portuguese)
Soliris (eculizumab)	***Information for physicians*** Guia do médico para prescrição em doentes com SHUa – 2.ª versão aprovada em maio de 2015 Guia do médico para prescrição em doentes com HPN – 3.ª versão aprovada em maio de 2015 ***Information for patients*** Brochura Informativa do Doente (Pais Cuidadores) com SHUa – 2.ª versão aprovada em maio de 2015 Brochura Informativa do Doente (Pais Cuidadores) com HPN – 3.ª versão aprovada em maio de 2015 Cartão de Informação de Segurança do Doente – 3.ª versão aprovada em maio de 2015
Tracleer (bosentan)	***Information for physicians*** Informação e orientações para o prescritor – 3.ª versão aprovada em agosto de 2015 For prescribing doctors specialized in internal medicine, cardiology, pneumology, rheumatology, and vascular surgery. ***Information for patients*** Orientações para o doente para uma utilização segura de Tracleer – 3.ª versão aprovada em agosto de 2015 To be handed out to the patient by the prescribing physician. Cartão de aviso do doente – 3.ª versão aprovada em agosto de 2015
Xeomin (botulinum toxin type A)	***Information for physicians*** Informação importante de segurança para médicos sobre o tratamento com Xeomin – 4.ª versão aprovada em maio de 2015 For rehabilitation medicine and neurology specialists. ***Information for patients*** Ficha de informação de segurança para o doente – 4.ª versão aprovada em maio de 2015
Xiapex (collagenase *Clostridium histolyticum*)	***Information for physicians*** Brochura educacional dirigida aos médicos - administração de Xiapex na doença de PEYRONIE - 1ª versão aprovada em junho de 2015 For urologists.

Compiled by Magda Pedro

Communications to Healthcare Professionals (June to August 2015)

Medicinal product	Click on topic for details (in Portuguese)
Anapen (adrenaline)	Always carry 2 units of auto-injector and seek urgent medical help.
Daklinza / Harvoni / Sovaldi	Risk of clinically significant arrhythmia when Harvoni (sofosbuvir+ledipasvir), or Daklinza (daclatasvir) in association with Sovaldi (sofosbuvir) are given concomitantly with amiodarone.
InductOs (Dibotermin alfa)	Possible scarcity of InductOs 1.5 mg/ml powder, solvent and matrix for implantation.
SGLT2 inhibitors (Forxiga, Xigduo, Invokana, Vokanamet, Jardiance, Synjardy)	Risk of diabetic ketoacidosis.
Kineret (anakinra)	Presence of solid material visible on the needle surface.

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
- **OR:**

INFARMED, I.P. – Direção de Gestão do Risco de Medicamentos
Risk Management Dpt.
Tel: +351 217 987 140; +351 217 987 141
Fax: +351 217 987 397
E-mail: farmacovigilancia@infarmed.pt

Unidade de Farmacovigilância do Norte
Northern Portugal Regional Pharmacovigilance Unit
Faculdade de Medicina da Universidade do Porto
Rua Doutor Plácido da Costa – 4200-450 Porto
Tel: +351 220 426 952/220 426 943 – Fax: +351 225 513 682
E-mail: ufn@med.up.pt
Site: www.ufn.med.up.pt

Unidade de Farmacovigilância de Lisboa e Vale do Tejo
Lisbon and Tagus Valley Regional Pharmacovigilance Unit
Laboratório de Farmacologia Clínica e Terapêutica
Faculdade de Medicina da Universidade de Lisboa
Av. Prof. Egas Moniz – 1649-028 Lisboa
Tel: +351 217 802 120/7; Ext. 44136/7 – Fax: +351 217 802 129
E-mail: uflvt@sapo.pt

Unidade de Farmacovigilância do Centro
Central Portugal Regional Pharmacovigilance Unit
AIBILI
Azinhaga de Santa Comba, Celas – 3000-548 Coimbra
Tel: +351 239 480 138 – Fax: +351 239 480 117
E-mail: ufc@aibili.pt
Site: http://aibili.pt/ufc_about.php

Unidade de Farmacovigilância do Sul
Southern Portugal Regional Pharmacovigilance Unit
Faculdade de Farmácia da Universidade de Lisboa
Av. das Forças Armadas – 1649-019 Lisboa
Tel./Fax: +351 217 971 340
E-mail: ufs@ff.ulisboa.pt
Site: http://ufs.ff.ul.pt

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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