boletim de FARMACOVIGILÂNCIA

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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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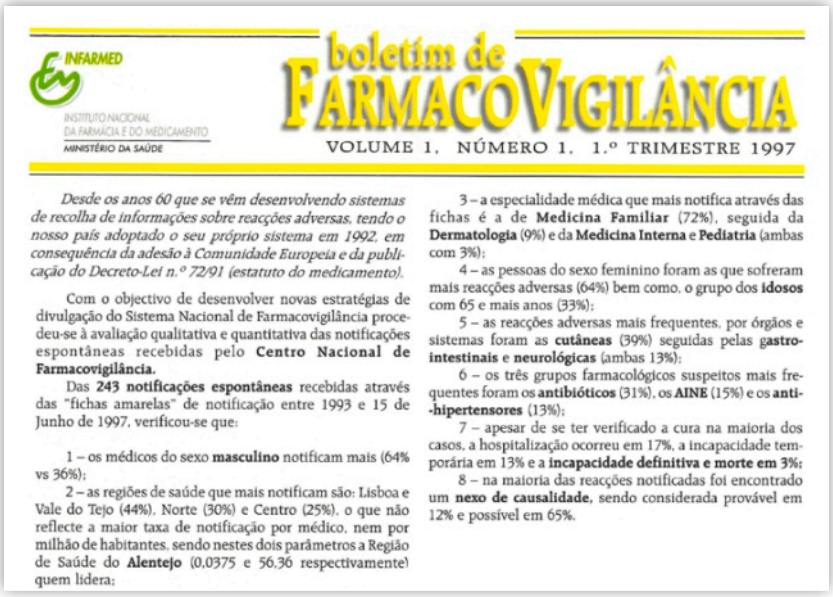
From the Editor

Volume 20 years of Pharmacovigilance Bulletin

In addition to the usual sections in this issue you will find: topical fusafungine withdrawal on account of negative risk-benefit ratio; favourable balance confirmed for inhaled corticosteroids; hormonal changes with the adrenal cytotoxic agent mitotane; risk of intestinal obstruction from adhesions with biological haemostatic "glue". A recently published review on common adverse effects and drug interactions with immunosuppressive therapy for transplant patients is also highlighted.

The European Medicines Agency is starting public hearings open to all EU citizens. This reflects a trend in the evolution of European pharmacovigilance systems.

The opening article in this issue of the Boletim gives an overview of ADR reporting in the year 2015 in Portugal, this being the year the five thousand report mark was overtaken. Twenty years ago, at the time the Boletim's first issue came out, the Portuguese system was only receiving an annual average of less than one hundred ADR reports and this is what the Boletim looked like:



INFARMED
INSTITUTO NACIONAL DA FARMÁCIA E DO MEDICAMENTO
MINISTÉRIO DA SAÚDE

boletim de FARMACOVIGILÂNCIA

VOLUME 1. NÚMERO 1. 1.º TRIMESTRE 1997

Desde os anos 60 que se vêm desenvolvendo sistemas de recolha de informações sobre reacções adversas, tendo o nosso país adoptado o seu próprio sistema em 1992, em consequência da adesão à Comunidade Europeia e da publicação do Decreto-Lei n.º 72/91 (estatuto do medicamento).

Com o objectivo de desenvolver novas estratégias de divulgação do Sistema Nacional de Farmacovigilância procedeu-se à avaliação qualitativa e quantitativa das notificações espontâneas recebidas pelo **Centro Nacional de Farmacovigilância.**

Das **243 notificações espontâneas** recebidas através das "fichas amarelas" de notificação entre 1993 e 15 de Junho de 1997, verificou-se que:

1 – os médicos do sexo **masculino** notificam mais (64% vs 36%);

2 – as regiões de saúde que mais notificam são: Lisboa e Vale do Tejo (44%), Norte (30%) e Centro (25%), o que não reflecte a maior taxa de notificação por médico, nem por milhão de habitantes, sendo nestes dois parâmetros a Região de Saúde do **Alentejo** (0,0375 e 56,36 respectivamente) quem lidera;

3 – a especialidade médica que mais notifica através das fichas é a de **Medicina Familiar** (72%), seguida da **Dermatologia** (9%) e da **Medicina Interna** e **Pediatria** (ambas com 3%);

4 – as pessoas do sexo feminino foram as que sofreram mais reacções adversas (64%) bem como, o grupo dos **idosos** com 65 e mais anos (33%);

5 – as reacções adversas mais frequentes, por órgãos e sistemas foram as **cutâneas** (39%) seguidas pelas **gastro-intestinais** e **neurológicas** (ambas 13%);

6 – os três grupos farmacológicos suspeitos mais frequentes foram os **antibióticos** (31%), os **AINE** (15%) e os **anti-hipertensores** (13%);

7 – apesar de se ter verificado a cura na maioria dos casos, a hospitalização ocorreu em 17%, a incapacidade temporária em 13% e a **incapacidade definitiva e morte em 3%;**

8 – na maioria das reacções notificadas foi encontrado um **nexo de causalidade**, sendo considerada provável em 12% e possível em 65%.

Safety alerts (recent and current) issued by Infarmed:

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

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Director:
Fátima Canedo

Editor:
Rui Pombal

Assistant Editor:
Leonor Nogueira Guerra

Contributors:
Ana Sofia Martins
António Leandro Ponte
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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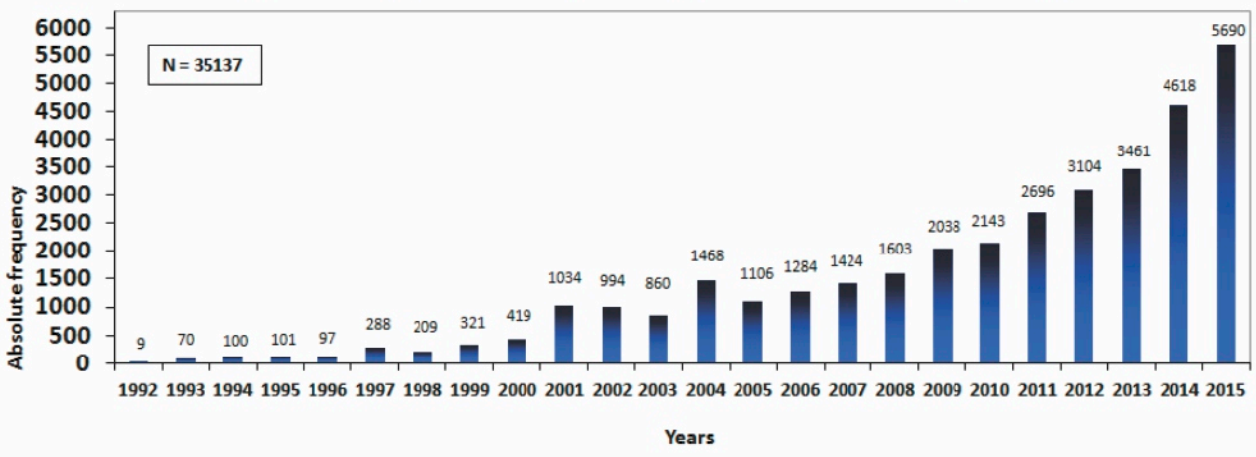
ADR Reports Year 2015

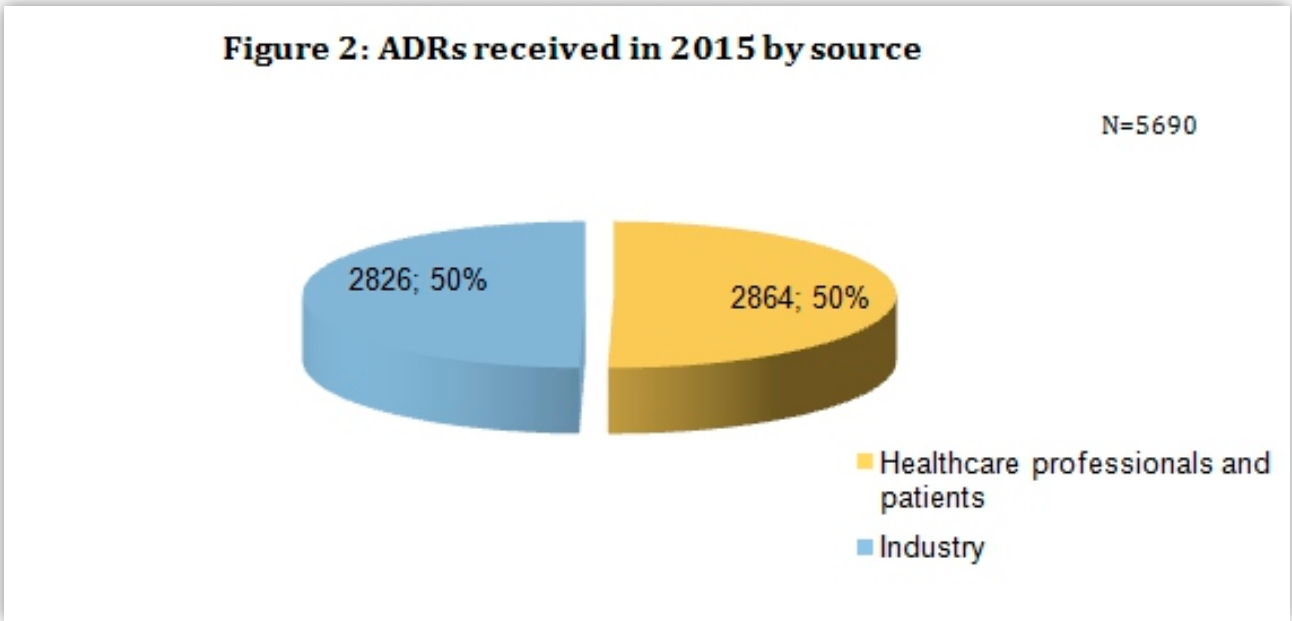
Culminating a growing trend since 2005, the Portuguese National Pharmacovigilance System received in 2015 a total of 5,690 **ADR** reports (Fig. 1). This corresponded to a 23% increase from 2014.

Figure 1: ADR reports received by the Portuguese National Pharmacovigilance System



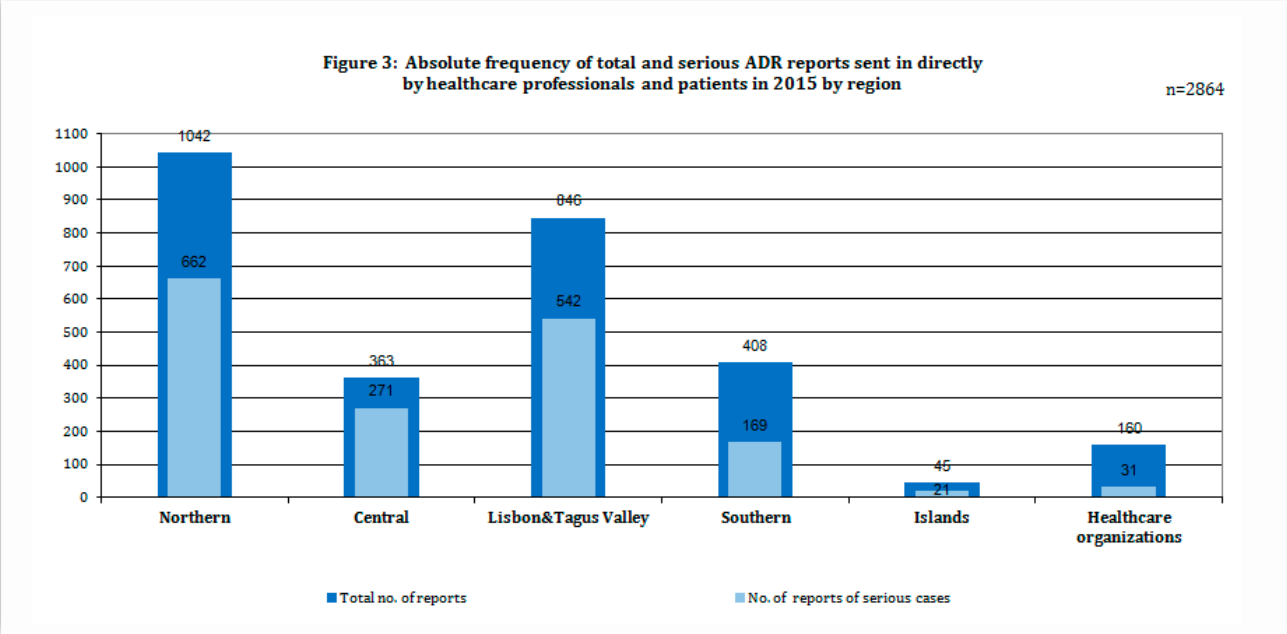
Of those 5,690 **ADR** reports 2,864 were sent in directly by healthcare professionals and patients, the other half having been received from **MA** Holders ("the industry") (Fig. 2).

Figure 2: ADRs received in 2015 by source

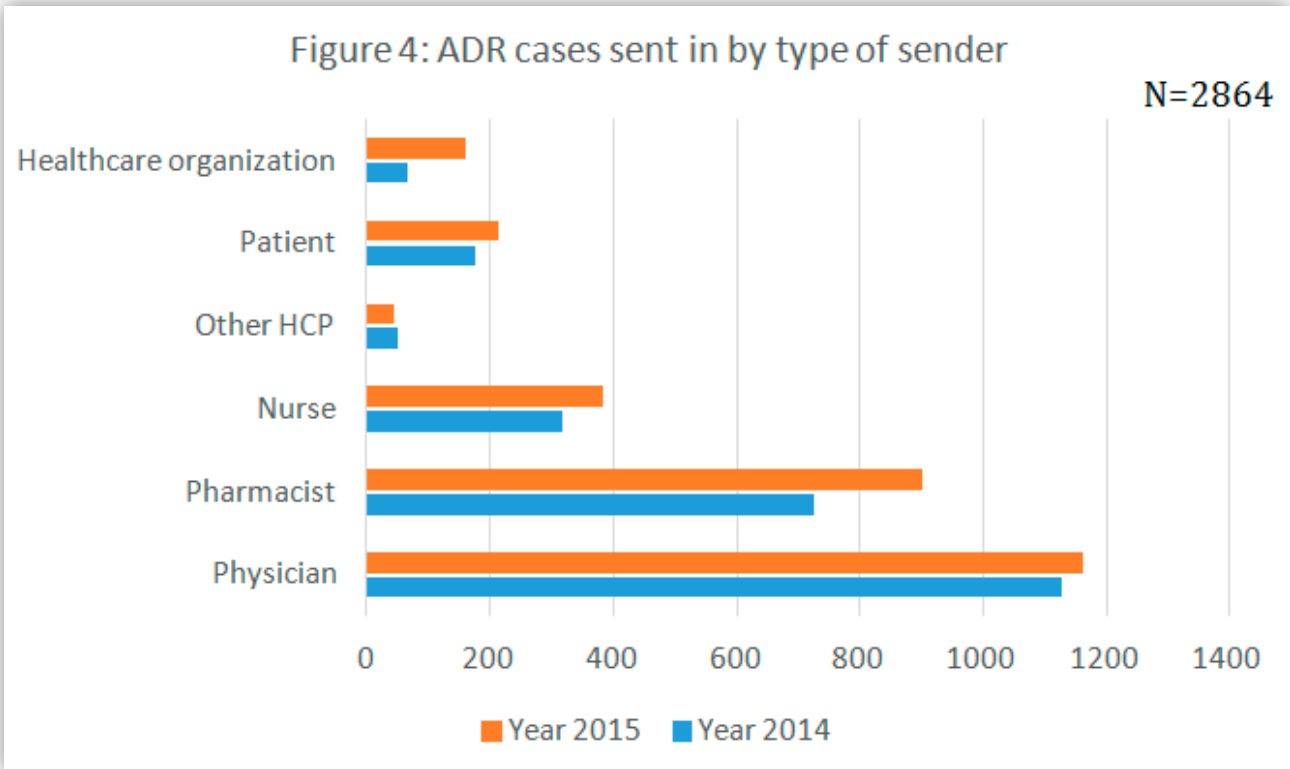


Fifty-nine percent (1,696) of the reports received from healthcare professionals and patients were serious cases, compared to 99% (2,795) from the industry. This is not unexpected since, with few exceptions, **MA** Holders are only legally required to report serious **ADR**s.

The geographical distribution and the relative proportion of serious cases within the reports sent in directly by healthcare professionals and patients is shown in Fig. 3.



In 2015, doctors made 41% of reports, followed by pharmacists (31%) and nurses (13%). Fig. 4 shows the variation per type of healthcare professional in relation to the preceding year.



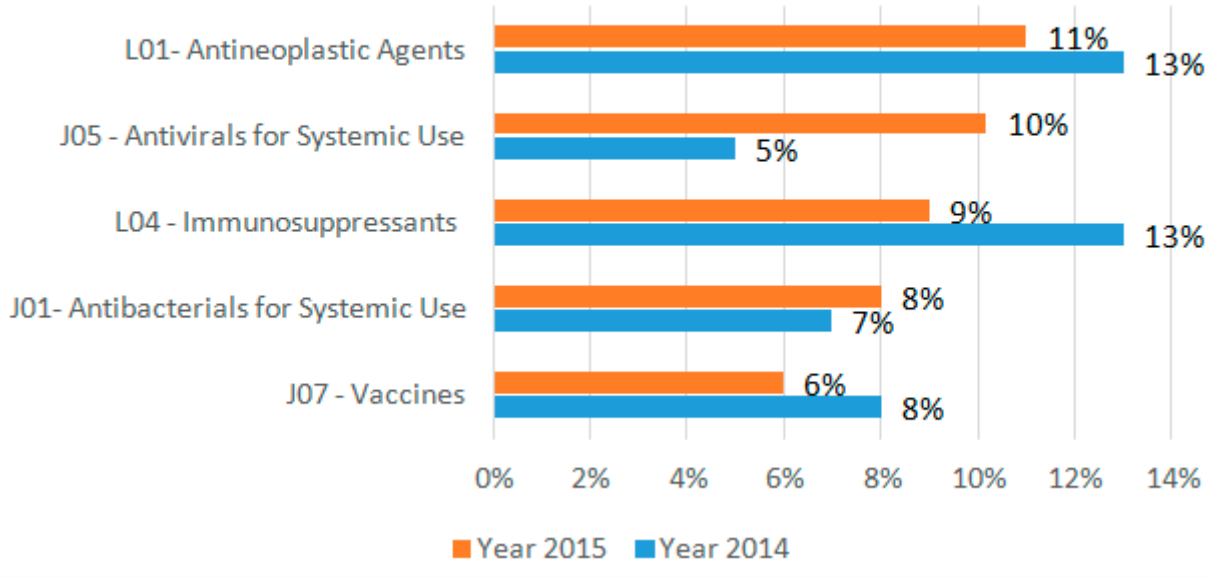
After weeding out the duplicates among the 5,690 reports, a total of **4,949 cases of ADR** were found. This means 13% of all reports had been duplicates. Duplicates can typically be originated from simultaneous reporting of one case by the healthcare professional and the MA Holder, for instance.

MedDRA, the *Medical Dictionary for Regulatory Activities*, lays out System Organ Class (SOC) terms that can be used to categorize ADRs. For categorization purposes all the ADRs belonging to the same SOC in the same case were counted as one only. This was done because often in the same case there are several ADRs which are nothing more than detailed descriptors of the various signs and symptoms of one given entity / condition.

A total of 9,826 occurrences of distinct SOCs was obtained. Just like in the preceding year, in 2015 the following SOCs predominated: *General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Nervous system disorders and Gastrointestinal disorders*. These four SOCs accounted for as much as 48% of the total, the remaining 52% being distributed across the other twenty-two SOCs.

The ATC (*Anatomical Therapeutic Chemical*) classes of the suspect or interacting medicinal products involved were analyzed as well. The 4,949 ADR cases involved medicines belonging to 80 different ATCs. The five most prevalent ATCs accounted for 48% of all the cases. In comparison with 2014, the most prevalent ATCs were the same albeit in slightly different relative positions (Fig. 5).

Figure 5: Relative frequency of most prevalent ATCs for the suspect or interacting medicines (N= 2551; 43% of overall total)



António Leandro Ponte, Leonor Nogueira Guerra, Fátima Hergy

Locabiosol® (fusafungine)
withdrawn

Quick Read

Infarmed, in cooperation with the MA Holder, has withdrawn Locabiosol 125 mcg® (fusafungine) in both oral and nasal spray solutions. This decision stems from an identified risk of serious allergic reactions against a backdrop of limited evidence of therapeutic benefits.

Fusafungine was indicated as a topic for upper airways conditions such as rhinopharyngitis, in the absence of clinical signs of generalized bacterial infection. It was deemed to have antibacterial and anti-inflammatory activity linked with macrophage and T lymphocyte pro-inflammatory modulating effects.

EMA has undertaken a safety review of topical fusafungine following an increase in the number of cases of serious allergic reactions, **including anaphylaxis**. Most serious cases included bronchospasm and occurred in adults and children immediately after use of the medication. Although these reactions are rare, they may be fatal and no measures could be identified to significantly minimize their risk.

Additionally, there were doubts concerning the benefits of fusafungine and its role in increasing bacterial resistance. EMA concluded that the beneficial effects of fusafangine are small, given the mild and self-limited nature of upper airways infections. The **risk-benefit ratio of this product is therefore negative** for all the indications approved in the EU. A recommendation ensued to revoke the marketing authorizations. This decision has been implemented in all the member states.

Margarida Guimarães

Inhaled Corticosteroids
Positive risk-benefit

Quick Read
Inhaled corticosteroids are still indicated for COAD, but a possible risk of pneumonia should be borne in mind, more so since its manifestations can mimic those of the background condition.

When inhaled corticosteroids reduce lower airways inflammation and are used for the treatment of chronic obstructive airways disease (COAD) via inhalation devices. In Portugal the available inhaled corticosteroids are budesonide and fluticasone.

A risk of pneumonia was identified in 2007 following the publication of a study that showed that patients with COAD treated with inhaled fluticasone had an increased risk of developing pneumonia as compared to placebo. Since then, several studies have been undertaken with other inhaled corticosteroids.

Although patients with COAD treated with inhaled corticosteroids present a higher risk of pneumonia, **PRAC** has concluded that their benefits still outweigh the risks. Additionally, no differences in pneumonia risk have been found among the various corticosteroids assessed.

Doctors and patients with COAD should be aware of the possibility of occurrence of signs and symptoms of pneumonia which may be mistaken for an exacerbation of the underlying disease.

Margarida Guimarães

Mitotane (Lysodren®)
Hormonal changes and ovarian cysts

Quick Read

Exposure to mitotane for several months may be associated with the appearance of ovarian cysts together with ovarian and gonadotropic hormonal changes.

Mitotane is a cytotoxic adrenal agent of unknown biochemical mechanism of action, which seems to be able to modify the peripheral metabolism of steroids and to directly suppress the adrenal cortex. It is indicated in the symptomatic treatment of advanced (non-resectable, metastatized or recurrent) adrenortical carcinoma.

Based on routine pharmacovigilance data and literature cases,[1,2] **EMA** raised a safety signal regarding the use of mitotane and changes in sex hormones and development of ovarian cysts. One article describes the occurrence of macrocysts in 21 **premenopausal** women, median age 33 years (range: 18-45 years), who took mitotane for the treatment of adrenocortical carcinoma or of Cushing's disease. The cysts were detected **after** a median time of 11 months (range: **3-36 months**) of exposure to mitotane and were **bilateral** in **51%** of cases. They were accompanied by hormonal changes, including a **significant decrease in the levels of androstenedione and testosterone** and a **significant rise of LH**.

The Portuguese versions of the texts to be implemented in the **SmPC** and **PIL** can be found here:

http://www.ema.europa.eu/docs/pt_PT/document_library/Other/2016/03/WC500202894.pdf

Leonor Chambel

[1] *Salenave S et al. Ovarian macrocysts and gonadotrope-ovarian axis disruption in premenopausal women receiving mitotane for adrenocortical carcinoma or Cushing's disease. Eur J Endocrinol. 2015 Feb;172(2):141-9. doi: 10.1530/EJE-14-0670. Epub 2014 Nov 19.*

[2] *Daffara F et al. Prospective evaluation of mitotane toxicity in adrenocortical cancer patients treated adjuvantly. Endocr Relat Cancer. 2008 Dec;15(4):1043-53.*

TachoSil®
Preventing intestinal obstruction caused by adhesions

Quick Read
The haemostatic "glue" TachoSil® used in surgery may be associated with the occurrence of intestinal obstruction caused by adhesions.

Tachosil® (human fibrinogen, human thrombin) is indicated in adults for surgical treatment support by promoting haemostasis and tissue adhesion, as well as for vascular surgery suture support when standard techniques are insufficient.

EMA raised a safety signal last May following the publication of a case of intestinal obstruction ascribed to this medicinal product and subsequent detection of other cases in EudraVigilance, the European adverse reaction database.[1] Taking into account all the available data, **EMA** has concluded that intestinal obstruction is a possible undesirable effect of Tachosil®.

The Portuguese version of the texts to be implemented in the **SmPC** (sections 4.4, 4.8 and 6.6) and **PIL** are available at Recomendações do **PRAC** decorrentes de avaliação de sinais de segurança –Highlights:

➜ Due to colegen's strong affinity for blood, TachoSil can also stick to **surgical instruments, surgical gloves or adjacent blood-covered tissues**. This can be avoided by cleansing before application.

➜ After pressing TachoSil onto the surgical wound, the **glove or swab** should be **carefully** removed. To prevent TachoSil from coming off it can be kept in place by holding it with a forceps tip, for instance.

Márcia Silva

[1] *Vázquez Ruiz J et al. Intestinal obstruction due to the use of a surgical hemostatic agent. Cir Esp. 2013 Nov;91(9):620-1*

European Medicines Agency
To start public hearings

The Pharmacovigilance Risk Assessment Committee (**PRAC**) of the European Medicines Agency (**EMA**) has decided to implement public hearings from September this year, and it has approved the rules for their conduct.

These public hearings will allow for **every EU citizen** to get involved in the supervision of medicinal products, by sharing their opinions and experience in what concerns the products' therapeutic effects and available alternatives. Patients will also have the opportunity to have their say regarding proposed risk management and minimization measures, thus being able to influence **PRAC**'s decision-making.

The hearings are to be decided on a case by case basis. All the details on the rules of the new procedure are available at this EMA page.

Margarida Guimarães

Transplanted patients: common adverse effects and drug interactions

In this useful American Journal of Medicine article, a top 10 is presented of what primary care physicians should know about maintenance immunosuppressive therapy in transplanted patients.

Even when stable, these patients are at increased risk for diarrhoea, urinary infections, erythrocytosis and osteonecrosis.
The table overleaf sums up the main **ADR**s and drug interactions to bear in mind, by type of immunosuppressive agent used.

mTOR inhibitors also inhibit wound healing. For that reason, discontinuation, dose reduction or switch to **calcineurin inhibitors** should be considered on a case by case basis before elective surgery.

These two groups of immunosuppressants are **metabolized by cytochrome CYP3A4**. Therefore, special care is necessary when co-administering or changing the dose of either CYP3A4 inhibitors (such as azole antifungals, protease inhibitors, macrolide antibiotics and calcium channel inhibitors) or inducers (such as rifampin, anticonvulsants, St John's wort).

The enzyme xanthine oxidase inactivates **azathioprine's** active metabolite 6-thioguanine, which explains why concomitant administration of xanthine oxidase inhibitors such as allopurinol is contraindicated. The same does not apply to mycophenolate since its metabolic pathways are completely different.

Agents such as mycophenolate, sirolimus or everolimus are teratogenic. Of the oral contraceptives, **progestagen-only formulations** should be favoured, in that oestrogens may affect the metabolism of calcineurin inhibitors.

Breastfeeding used to be advised against in the literature, but more recent data suggest that it may be safe when mothers are on prednisone, ciclosporin or tacrolimus.

Continues overleaf

ADRs in the Literature

Active ingredient	Common adverse effects
Calcineurin inhibitors (inhibit early T cell activation)	
Ciclosporin	**Acute renal injury, hyperkalaemia, hypomagnesaemia, hypertension, gengival hyperplasia, hirsutism**
Tacrolimus	**Acute renal injury, hyperkalaemia, hypomagnesaemia, tremor, diabetes, alopecia**
mTOR inhibitors (inhibit T cell activation and proliferation signaling)	
Sirolimus	**Poor healing, hyperlipaemia, interstitial pneumonitis, mouth ulcers, proteinuria, myelosuppression**
Everolimus	
Antimetabolites (prevent lymphocyte proliferation by interfering with nucleotide synthesis)	
Azathioprine	**Myelosuppression, skin rash, cholestatic jaundice**
Mycophenolate	**Myelosuppression, GI toxicity**
Corticosteroids (antiinflamatory action)	
Prednisone	**Diabetes, fluid retention, hypertension, peptic ulcer, osteoporosis, avascular bone necrosis, hyperlipaemia**

Lien, Y-HH. Am J Med Vol 129(6), June 2016, 568–572.

Educational Materials published on the Infarmed website
(March to June 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Blincyto (blinatumomab)	***Information for prescribing physicians*** Material educacional para os médicos – 1.ª versão aprovada em fevereiro de 2016 ***Information for pharmacists*** Material educacional para o farmacêutico – 1.ª versão aprovada em fevereiro de 2016 For pharmacists involved in reconstituting and preparing the medicine. ***Information for patients*** Material educacional para o doente/cuidadores – 1.ª versão aprovada em fevereiro de 2016 Cartão de alerta para o doente – 1.ª versão aprovada em fevereiro de 2016
Coltramyl (thiocholchicoside)	***Information for physicians*** Guia para o prescritor sobre o medicamento Coltramyl – 1.ª versão aprovada em março de 2016 For family physicians, orthopaedic surgeons, rheumatologists, gynaecologists, rehabilitation medicine, internal medicine and occupational medicine specialists. ***Information for patients*** Cartão do doente sobre o medicamento Coltramyl – 1.ª versão aprovada em março de 2016
Deltyba (delamanid)	***Information for prescribing physicians*** Informações de segurança importantes para os profissionais de saúde – 1.ª versão aprovada em abril de 2016 ***Information for patients*** Utilizar Deltyba (delamanid) durante a gravidez ou a amamentação – 1.ª versão aprovada em abril de 2016
Eylea (aflibercept)	***Information for physicians*** Recomendações para o médico – 5.ª versão aprovada em novembro de 2015 For physicians with experience in intravitreal injection who may prescribe or administer this medicine. ***Information for patients*** Guia do doente com perda de visão devido a neovascularização coroideia associada a miopia patológica (NVC miópica) - 1ª versão aprovada em novembro de 2015

Educational Materials published on the Infarmed website
(March to June 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Eziclen (association of sodium sulfate, magnesium sulfate and potassium sulfate)	***Information for physicians*** Folheto para o médico - 2ª versão aprovada em março de 2016 For general practitioners and gastroenterologists. ***Information for patients*** Formulário de instruções e registo - 2ª versão aprovada em março de 2016
Gilenya (fingolimod)	***Information for physicians*** Guia e lista de verificação do médico prescritor - 6ª versão aprovada em fevereiro de 2016 For neurologists. ***Information for patients*** Cartão de informação para o doente - 6ª versão aprovada em fevereiro de 2016
Humira (adalimumab)	***Information for patients*** Guia de Administração para doentes em tratamento com Humira – 4.ª versão aprovada em fevereiro de 2016
Isotretinoína Aurovitas (isotretinoin)	***Information for physicians*** Comunicação ao médico - 3ª versão aprovada em abril de 2016 Guia do médico para a prescrição de isotretinoína - 3ª versão aprovada em abril de 2016 Checklist do médico para prescrição de isotretinoína a doentes do sexo feminino - 3ª versão aprovada em abril de 2016 Formulário de notificação/acompanhamento de gravidez em doente tratada com Isotretinoína Aurovitas - 3ª versão aprovada em abril de 2016 Formulário de consentimento informado para as doentes do sexo feminino - 3ª versão aprovada em abril de 2016 Formulário de consentimento informado geral – 1.ª versão aprovada em abril de 2016 For dermatologists and family physicians. ***Information for pharmacists*** Comunicação ao farmacêutico – 3.ª versão aprovada em abril de 2016 Guia do farmacêutico para a dispensa de isotretinoína – 3.ª versão aprovada em abril de 2016 ***Information for patients*** Guia do doente para a utilização de isotretinoína – 3.ª versão aprovada em abril de 2016

Educational Materials published on the Infarmed website
(March to June 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Jetrea (ocriplasmin)	***Information for patients*** Guia de tratamento com Jetrea – 3.ª versão aprovada em fevereiro de 2016
Lemtrada (alemtuzumab)	***Information for physicians*** Guia do profissional de cuidados de saúde – 1.ª versão aprovada em abril de 2014 Lista de verificação para o prescritor – 1.ª versão aprovada em abril de 2014 For neurologist prescribers. ***Information for patients*** Cartão de alerta do doente – 1.ª versão aprovada em abril de 2014 Guia do doente – 1.ª versão aprovada em abril de 2014
Myozyme (alglucosidase alfa)	***Information for healthcare professionals*** Guia para os profissionais de saúde sobre os riscos associados à administração, a gestão do risco clínico e os testes de imunogenicidade – 4.ª versão aprovada em fevereiro de 2016 For doctors, nurses and pharmacists involved in the treatment of Pompe's disease.
Revolade (eltrombopag)	***Information for physicians*** Guia de Segurança de REVOLADE (eltrombopag) na trombocitopenia associada à hepatite C crónica (TaVHC) - 4ª versão aprovada em abril de 2016 Guia de Segurança do REVOLADE (eltrombopag) na púrpura trombocitopénica idiopática (PTI) crónica - 1ª versão aprovada em abril de 2016 For gastrenterologists. ***Information for patients*** Guia para Doentes sobre o REVOLADE (eltrombopag) na púrpura trombocitopénica imune (idiopática) (PTI) - 1ª versão aprovada em abril de 2016 Guia para Doentes sobre o REVOLADE (eltrambopag) na trombocitopenia associada à hepatite C crónica (TaVHC) - 1ª versão aprovada em abril de 2016
Strensiq (asfotase alfa)	***Information for patients*** Guia de autoinjeção – 1.ª versão aprovada em fevereiro de 2016 Guia de injeção – Pais/Acompanhantes de crianças – 1.ª versão aprovada em fevereiro de 2016

Educational Materials published on the Infarmed website
(March to June 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Vectibix (panitumumab)	***Information for physicians*** Folheto educacional para médicos oncologistas – 7.ª versão aprovada em fevereiro de 2016
Volibris ambrisentan	***Information for physicians*** Informação para o profissional de saúde – 4.ª versão aprovada em março de 2016 Check-list pré-prescrição – 4.ª versão aprovada em março de 2016 Formulário de notificação inicial de gravidez – 4.ª versão aprovada em março de 2016 Formulário de notificação de termo de gravidez – 4.ª versão aprovada em março de 2016 Formulário de notificação de reações adversas – 4.ª versão aprovada em março de 2016 ***Information for patients*** Brochura informativa para os doentes – 4.ª versão aprovada em março de 2016 Cartão de memória do doente - 4ª versão aprovada em março de 2016 Information for male partners of women of childbearing age being treated with ambrisentan Brochura informativa para o parceiro masculino de mulheres em idade fértil – 4.ª versão aprovada em março de 2016
Xalkori (crizotinib)	***Information for healthcare professionals*** Informação de segurança importante sobre a utilização de crizotinib para Profissionais de Saúde – 4.ª versão aprovada em março de 2016 For pneumologists and oncologists who treat lung cancer, and for hospital pharmacists. ***Information for patients*** Guia para o doente – 4.ª versão aprovada em março de 2016

Educational Materials published on the Infarmed website
(March to June 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Xiapex (collagenase clostridium histolyticum)	***Information for physicians*** Brochura educacional dirigida aos médicos - administração de Xiapex na contratura de Dupuytren - 2ª versão aprovada em março de 2016 For physicians experienced in the diagnosis and treatment of Dupuytren's: plastic surgeons and orthopaedic surgeons.
Zalviso (sufentanil)	***Information for physicians*** Guia de administração para os profissionais de saúde – 1.ª versão aprovada em março de 2016 For potential prescribers (specialized in anaesthetics, general surgery, ophthalmology, Ob/Gyn, ENT, dentistry, plastic surgery, dermatology, urology, vascular surgery, neurosurgery, cardiothoracic surgery), as well as for head nurses and pharmacists in hospitals concerned.

Compiled by Magda Pedro

Communications to Healthcare Professionals (March to June 2016)

Medicinal product (DCI)	Click on topic for details (in Portuguese)
Imnovid (pomalidomide)	Determine phase of chronic hepatitis B virus infection before starting treatment
SGLT2 inhibitors (Forxiga, Xigduo, Invokana, Vokanamet, Jardiance, Synjardy)	Risk of diabetic ketoacidosis
Ketoconazole HRA (Ketoconazole)	Risk of hepatotoxicity
Locabiosol (fusafungine)	Market withdrawal
Primene 10% (aminoacids)	Precipitation following preparation of solutions for infusion
Noxafil (posaconazole)	Sodium quantity mismatch between the SmPC and the PIL
Taxotere (docetaxel)	Voluntary recall, risk of overdose, and interruption of supply
Thalidomide Celgene (thalidomide)	Viral reactivation and pulmonary hypertension
Tysabri (natalizumab)	Update on minimization of risk of progressive multifocal leucoencephalopathy
Viternum (dihexazin)	Medication errors
Xofigo (radium dichloride)	Change in NIST Standard Reference Material
Zaltrap (aflibercept)	Risk of osteonecrosis of the jaw
Zydelig (idelalisib)	Restrictions to use in the treatment of chronic lymphocytic leukaemia (CLL) and relapsing follicular lymphoma (FL)

Compiled by Ana Sofia Martins

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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