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From the Editor

It is intrinsic to the nature of adverse reactions that their risk cannot unfortunately be totally eliminated, even when it is well-known and characterized. This does not mean it cannot be managed, for example through risk minimization measures. Just like a mathematical function limit tends to a given value, those measures may help us to approach, even if at a considerable distance and by very small steps, an illusory "zero risk" goal.

Risk minimization is one of the current foci of medicines safety management and aims to use of the most robust evidence available. In some cases risk minimization is not possible or is marginal, in others it will have a significant impact. The measures that need to be taken are often not exceedingly complex to implement, such as the issuance of a specific safety alert to professionals and patients who use a given medicinal product.

As usual the current issue of the Boletim includes various instances of how risk minimization backed up by available relevant evidence: combined hormonal contraceptives and thromboembolism, agomelatin and liver injury, lithium and renal tumours, valproic acid and mithocondrial pathology.

Further in this issue: paroxetine (and other selective serotonin reuptake inhibitors) and aggressivity, vildagliptin and myalgia, ambroxol/bromhexine and serious skin reactions, IV amiodarone and syndrome of inappropriate antidiuretic hormone secretion.

Finally a reminder of the Infarmed Safety Alerts page:

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

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Combined Hormonal Contraceptives
Venous thromboembolism

Quick Read

Though small there is a known risk of venous thromboembolism associated with the use of combined hormonal contraceptives, especially during the first year of exposure and whenever they are resumed after discontinuation for at least one month. Periodical reassessment and patient education regarding risk factors and warning signs and symptoms are essential for keeping the benefits of undesired pregnancy prevention higher than the potential risk of thromboembolism.

Combined hormonal contraceptives (CHC) contain two types of hormones: an oestrogen and a progestagen. They have been subjected to several studies and the attending risk of **venous thromboembolim (VTE)** has been known for years. For the more recent, low-dose (ethinylestradiol <50µg) agents, risk is small. However, depending on the type of progestagen used, the various CHCs may show some differences (table below).

Risk of developping a blood clot (VTE) within one year[1]	
Women who do **not use** any combined hormonal pill/skin patch/ring and who are not pregnant	Circa 2 in 10,000 women
Women who use a CHC containing **evonorgestrel, norethisterone or norgestimate**	Circa 5 to 7 in 10,000 women
Women who use a CHC containing **etonogestrel or norelgestromin**	Circa 6 to 12 in 10,000 women
Women who use a CHC containing **drospirenone, gestodene or desogestrel**	Circa 9 to 12 in 10,000 women
Women who use a CHC containing **clormadinone, dienogest or nomegestrol**	Still not known[2]

VTE (fatal in 1-2%)[3] is a rare event in healthy young women and may have a non-specific presentation, making early diagnosis a challenge.

Known **risk factors** for VTE include, among other, positive past family history, pregnancy, age, trauma, surgery, prolonged immobilization, obesity, and smoking. **Risk** is **increased** in the **first year of use** or whenever treatment is **started again** after a period of non-use of at least one month.

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The **risk of arterial thromboembolism** (which can cause myocardial infarction and cerebrovascular accidents) is **also raised** with the use of CHCs. However, there are not sufficient data on whether and how this risk varies depending on different low-dose CHCs.

The following **key messages** are essential to bear in mind if one is to keep the benefits associated with the prevention of undesired pregnancies higher than the risk of VTE:

- When prescribing a CHC, special attention should be paid to the woman's risk factors and the varying risk of VTE with the diverse CHCs.
- CHCs are contraindicated in women who have one serious risk factor or multiple risk factors which place them at a high risk of blood clot formation.
- Each woman's risk factors vary with time. It is therefore necessary to periodically reassess the adequacy of the contraceptive agent.
- It is very important that women be informed and made aware of the risk of VTE and its signs and symptoms, which include severe leg pain or swelling, sudden unexplained breathlessness, sudden cough or accelerated breathing, chest pain, weakness, or numbness in the face, arms or legs.
- Healthcare professionals should consider the possibility of thromboembolism in women using CHCs who present with symptoms.

This information is reflected on the **SmPC** and **PIL** of these medicinal products to help healthcare professionals and women to take joint informed decisions when choosing a contraceptive method.

Ana Sofia Martins

[1] *Data from the latest European safety review in 2013.*

[2] *There are planned or ongoing studies aiming to collect data which will make risk estimation possible.*

[3] *Rosendaal, F.R. Venous thrombosis: a multicausal disease. Lancet. 1999; 353: 1167-73.*

Agomelatin
Minimizing the risk of liver injury

Quick Read

Liver function should be assessed and monitored before and during treatment with agomelatin.

Agomelatin is used for the treatment of major depressive episodes in adults. In Portugal only Valdoxan is marketed. The main associated safety issue is liver toxicity. Following a periodical safety update report, **EMA** concluded that the benefit/risk ratio remains favourable as long as measures are implemented to minimize the risk of hepatic injury.

Healthcare professionals should adopt the following recommendations which will be reflected on the **SmPC** and **PIL**:

- Before treatment is started, l**iver function tests** should be performed, and therapy should not be started if **transaminase levels** are **more than three times** above the upper limit of normal.
- **Liver function** should be **periodically monitored** throughout treatment (at 3, 6, 12, and 24 weeks, whenever clinically indicated thereafter).
- Treatment should be immediately **discontinued** in case the serum levels of **transaminases exceed more than three-fold** the upper limits of normal, or the patient presents signs or symptoms of potential liver injury.
- **Patients should be informed** about signs and symptoms of possible liver injury (dark urine, light stools, yellowish skin or eyes, pain in the upper abdomen, prolonged and unexplained fatigue) and the importance of monitoring their liver function. They should be advised to stop treatment and seek medical advice should symptoms appear.

Ana Sofia Martins

Paroxetine
Aggressivity?

Quick Read

Available evidence on the potential association between selective serotonin reuptake inhibitors (such as paroxetine) and aggressivity does not seem consistent, and both beneficial and harmful effects have been reported. **SmPC**/**PIL** are soon to be updated regarding this issue.

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depression, obsessive-compulsive disorder, panic disorder without agoraphobia, social anxiety / social phobia disorders, generalized anxiety disorder and posttraumatic stress disorder.

A possible association between the use of SSRIs and aggressivity is not a novel safety concern and has been under monitoring. **The SmPCs of all SSRIs include a warning regarding aggressivity in children and adolescents younger than 18 years**.

Various mechanisms have been identified which may explain some proneness to aggressivity from the use of SSRIs. Paroxetine may lower inhibition and agressivity can result. However, from pharmacovigilance data only it is difficult to conclude whether there is a definitive causal link between paroxetine and aggressivity, given confounding factors, such as the underlying condition and social circumstances. **Literature data** are conflicting and suggest both beneficial and harmful effects of SSRIs on aggressivity.[1-7]

PRAC agreed with the **MA** holder of Seroxat (paroxetine) on a review of all the reports of aggressivity or suggested aggressivity in adults from all sources, namely spontaneous reports, clinical trials and literature. Several small clinical trials suggest that SSRIs may reduce aggressive behavior in patients with a preexisting history of aggressive/violent behavior, while others demonstrate no such effect. In an observational study with antidepressants a reduction in the risk of violent behavior was noted, while in another study an association between ISSRs and violence was found.[8-11]

Based on the available data, **PRAC** recommended that the **MA** holders of all the medicinal products containing paroxetine submit to their national authorities an alteration to the **SmPC** and **PIL**. The Portuguese translations of the texts to be implemented will be available at Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Márcia Silva

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Lithium salts
Risk of renal tumours

Quick Read

Patients with severe renal impairment and who have been receiving lithium therapy for over 10 years may have an increased risk of renal microcysts, oncocytoma and collecting duct carcinoma.

The German medicines authority received in 2014 a clinical assessment report from an **MA** holder regarding a safety signal of a potential association between solid renal tumours and lithium therapy. Renal cell carcinoma accounts for about 2% of malignant neoplasms in adults.[1] The causes are unknown but some risk factors have been identified, such as smoking and family history.

Most of the fourteen cases included in the clinical assessment report concern patients who had been receiving lithium for 10 or more years. They all had chronic renal failure. Given the wide exposure of patients to lithium therapy, the number of cases was considered small, and the **PRAC** requested further exploration of the available data. Data from epidemiological studies showed that patients receiving lithium, when compared to the general population, had an increased risk of developing renal tumours, namely kidney cancer and oncocytoma. The histology results suggest that those tumours had originated in the collecting ducts.

PRAC considers that there is suficiente evidence for microcysts, oncocytoma and renal collecting duct carcinoma in patients with serious renal impairment and who have received lithium therapy for over 10 years. It therefore recommended an **SmPC** and **PIL** update – Portuguese versions here: Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Sílvia Duarte

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Vildagliptin
Risk of myalgia

Quick Read

There seems to be an increased incidence of myalgia associated with vildagliptin. Currently there is not sufficient evidence to support an association with rhabdomyolysis.

Vildagliptin is used in the treatment of type 2 diabetes. In Portugal six products are marketed, half of which also contain metformin.

Cases of rhabdomyolysis/myopathy and myalgia associated with products containing vildagliptin and vildagliptin + metformin have been spotted in routine safety signal detection activities. Although in some cases patients were also taking other drugs, the time relation between treatment with vildagliptin and a positive diagnosis made plausible an association between rhabdomyolysis/myalgia and this oral antiabetic agent. **PRAC** recommended a cumulative review of this issue. The benefit/risk ratio of vildagliptin was considered to remain positive; there is **not** sufficient evidence for an association between vildagliptin and **rhabdomyolysis.** However, the **SmPCs** and **PILs** are to be updated to include myalgia (especially in combination with statins), since:

- Patients taking vildagliptin in combination with statins, when compared to placebo, show a **higher incidence of myalgia**.
- Most cases of myalgia have been reported during the postmarketing phase.
- Data from the literature supports an association between musculoskeletal disorders and gliptins.
- In other medicines in the same class (sitagliptin and saxagliptin) there is already a reference to a risk of myalgia.

Ana Sofia Martins

Ambroxol e Bromhexine

Risk of serious allergic skin reactions

Quick Read

Though the risk is low, serious skin reactions can occur with the mucolytic agentes ambroxol and bromhexine.

PRAC has concluded a review on the risk of allergic reactions from medicinal products containing ambroxol or bromhexine, which are frequently used for their mucolytic effect. This review had been triggered by the Belgian medicines agency following cases of allergic reactions and **SCAR (serious cutaneous adverse reactions, including erythema multiforme, Stevens-Jonhson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis)** with ambroxol. This review also included bromhexine, since the latter is metabolized into ambroxol in the human body and some cases of allergic reactions have been reported in association with its use.

PRAC considers that the risk of allergic reactions (frequency unknown) is small, but has recommended that additional information on serious allergic reactions and SCAR as side effects be included in the **SmPCs** and **PILs**, including a warning to **immediately discontinue** the treatment should any manifestations of SCAR supervene.

Margarida Guimarães

Amiodarone
Risk of SIADH

Quick Read

It is possible that both the oral and the IV formulations of amiodarone may be associated with the syndrome of inappropriate antidiuretic hormone secretion.

SIADH (syndrome of inappropriate antidiuretic hormone secretion) is already included in the **SmPC** and **PIL** of the oral formulations of amiodarone, though not in those of the intravenous (IV) formulations.

A question has recently been raised whether this type of adverse effect also applies to IV formulations. Though its mechanism has not yet been clarified, an association between amiodarone and SIADH is supported by several authors.[1-13] Given the current data, it is possible that both the oral and the IV formulations may be involved in the appearance of this reaction.

Based on an analysis of the available data, **PRAC** recommended in February 2015 that the **MA** holders of IV formulations of amiodarone submit changes to their **SmPCs** (section 4.8) and **PILs** (section 4), in order to include SIADH. These changes can be looked up here:

http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2015/03/WC500183738.pdf

Leonor Chambel

[1] Grecian R et al. Acute hepatic failure following intravenous amiodarone. BMJ Case Reports 2012 Dec 18;2012.

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Valproate
Risk of mithocondrial toxicity

Quick Read

Valproic acid should be the last treatment choice for epilepsy in patients with mitochondrial conditions. Moreover, patients with POLG mutations are at increased risk of liver toxicity.

Mithocondrial diseases (MD) are predominantly but not exclusively due to cell respiratory chain dysfunction (more frequently hereditary than acquired). Symptoms are protean and may include weak motor control, muscular weakness and pain, gastrointestinal disease, developmental delay, heart disease, liver disease, diabetes mellitus, respiratory disease, seizures, visual/hearing impairment, lactic acidosis and susceptibility to infections. MDs are an important cause of **epilepsy and seizures**.

Valproate is used for the treatment of epilepsy and bipolar disease, as well as for migraine prophylaxis.

Antiepileptic agents with mithocondrial toxicity can trigger or worsen mithocondrial pathology with risk of death. In comparative studies, valproic acid was the drug that presented the greatest potential to interfere with the mithochondrial pathways. For this reason, it should be the **last choice for the treatment of epilepsy in patients with MD**. MD guidelines already reflect this recommendation.[1-9]

The FDA (US Food and Drug Administration) issued a safety alert in 2013 on an **increased risk of liver failure** induced by valproate in patients with hereditary neurometabolic syndromes caused by mutations in the **POLG** gene codifying the mitochondrial enzyme DNA polymerase gamma. Additionally, valproate is contraindicated in patients with mitochondrial disease caused by POLG mutations and in children younger than 2 years with a clinical suspicion of mitochondrial pathology.

Following a recent assessment, the European Pharmacogenomics Working Party has confirmed that there is sufficient evidence to justify a contraindication in patients with mitochondrial diseases caused by **POLG mutations**, and suggested a further **contraindication** in **children younger than 2 years who are suspected to have a POLG-related condition**.

PRAC has concluded that there is sufficient evidence to support a causal association between valproate and the worsening of underlying mitochondrial disease, including a risk of hepatotoxicity mainly in patients with POLG mutations. The Portuguese versions of the ensuing updated texts to be implemented in the **SmPCs** and **PILs** are available here:

Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Márcia Silva

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Educational Materials published on the Infarmed website
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Medicinal product	Click on the links (in Portuguese)
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Ciproterona + Etinilestradiol Generis (ciproterone + ethinylestradiol)	***Information for physicians*** Lista de Verificação para Prescritores - 1ª versão aprovada em novembro de 2014 For general/family medicine, gynaecology and dermatology specialists. ***Information for patients*** Cartão de Informação para a Doente - 1ª versão aprovada em novembro de 2014
Defitélio (defibrotide)	***Information for physicians*** Informações sobre um registo de doentes - 1ª versão aprovada em setembro de 2014 To be presented during visits to physicians in transplantation centres. Informação importante para médicos prescritores - 1ª versão aprovada em setembro de 2014 For physicians who prescribe and/or order Defitélio.

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Eliquis (apixaban)	***Information for physicians*** Guia do prescritor - 3ª versão aprovada em novembro de 2014 For physicians who may prescribe/use Eliquis, namely cardiologists, neurologists, internists, family physicians and haematologists. ***Information for patients*** Cartão de alerta do doente - 3ª versão aprovada em novembro de 2014

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IV Iron (Cosmofer, Ferinject, Monofar, Óxido Férrico Sacarosado Combino, Óxido Férrico Sacarosado Generis, Referen, and Venofer)	***Information for healthcare professionals*** Carta de rosto da 1.ª versão dos materiais educacionais Informação essencial de prescrição e administração para minimizar o risco de reações graves de hipersensibilidade – 1.ª versão aprovada em novembro de 2014 For clinical directors of public and private hospitals and haemodialysis clinics, heads of nephrology, gastroenterology, ob-gyn, orthopaedics, internal medicine, immunohaemotherapy and haematology departments, heads of GP healthcentres, heads of (public and private) hospital pharmaceutical services. ***Information for patients*** Informação de segurança importante para os doentes sobre possíveis reações alérgicas ao Ferro IV (medicamentos com ferro administrados por via intravenosa) – 1.ª versão aprovada em novembro de 2014

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Kivexa (abacavir)	***Information for physicians*** Informação de Segurança: Reações de Hipersensibilidade Graves Associadas à Utilização de Abacavir – 2.ª versão aprovada em novembro de 2014 For physicians who treat HIV/AIDS patients, as well as for corresponding patient associations.
Nexobrid (bromelain)	***Information for healthcare professionals*** Informação de segurança dirigida aos profissionais de saúde em unidades especializadas para queimados que poderão utilizar e/ou prescrever o medicamento Nexobrid – 1.ª versão aprovada em agosto de 2014 For burn unit healthcare professionals.
Opsumit (macitentan)	***Information for healthcare professionals*** Brochura para profissionais de saúde: informação de segurança importante – 1.ª versão aprovada em agosto de 2014 For prescribing physicians who specialize in the treatment of arterial pulmonary hypertension and for pharmacists in services procuring this medicinal product. Lista de verificação de prescrição – 1.ª versão aprovada em agosto de 2014 For prescribing physicians who specialize in the treatment of arterial pulmonary hypertension.

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Medicinal product	Click on the links (in Portuguese)
Revolade (eltrombopag)	***Information for physicians*** Capa do guia para o médico – 3.ª versão aprovada em março de 2014 Guia para o médico – 3.ª versão aprovada em março de 2014 For gastroenterologists. ***Information for patients*** Guia para o doente – 3.ª versão aprovada em março de 2014
Soliris (eculizumab)	***Information for physicians*** Guia do médico para prescrição em doentes com SHUa - 2ª versão aprovada em agosto de 2014 Guia do médico para prescrição em doentes com HPN – 2.ª versão aprovada em agosto de 2014 Guia do médico para prescrição em doentes com SHUa – 2.ª versão aprovada em agosto de 2014 Certificado de Vacinação – Antibióticos Profiláticos – 3.ª versão aprovada em janeiro de 2015 Certificado de Revacinação – 1.ª versão aprovada em fevereiro de 2015 ***Information for patients*** Brochura Informativa do Doente (Pais Cuidadores) com SHUa - 2ª versão aprovada em agosto de 2014 Brochura Informativa do Doente (Pais Cuidadores) com HPN – 2.ª versão aprovada em agosto de 2014 Cartão de Informação de Segurança do Doente – 2.ª versão aprovada em agosto de 2014
Sonovue (sulfur hexafluoride)	***Information for physicians and users*** Sonovue – Material educacional/Informação para médicos e utilizadores – 3.ª versão aprovada em outubro de 2014
Stelara (Ustecinumab)	***Information for healthcare professionals*** Informação de segurança importante para o profissional de saúde – 5.ª versão aprovada em fevereiro de 2015 For dermatologists and rheumatologists, hospital pharmacists and nurses. ***Information for patients*** Informação de segurança para o doente – 5.ª versão aprovada em fevereiro de 2015

Educational Materials published on the Infarmed website
(December 2014 to February 2015)

Medicinal product	Click on the links (in Portuguese)
Tarceva (Erlotinib, cloridrato)	***Information for physicians*** Informação para o prescritor – 2.ª versão aprovada em outubro de 2014 For oncologists and respiratory medicine specialists.
Triumeq (abacavir)	***Information for physicians*** Informação de segurança: reações de hipersensibilidade graves associadas à utilização de Abacavir – 2.ª versão aprovada em novembro de 2014 For physicians who treat HIV/AIDS patients, as well as for corresponding patient associations.
Trizivir (abacavir)	***Information for physicians*** Informação de segurança: reações de hipersensibilidade graves associadas à utilização de Abacavir – 2.ª versão aprovada em novembro de 2014 For physicians who treat HIV/AIDS patients, as well as for corresponding patient associations
Tygacil (tigecycline)	***Information for healthcare professionals*** Programa Educacional de Tygacil (tigeciclina) – 1.ª versão aprovada em janeiro de 2012 For hospital pharmacists and dermatologists, surgeons, intensive care specialists, infectious diseases specialists and microbiologists.
Valdoxan (agomelatin)	***Information for physicians*** Informação de segurança para os profissionais de saúde – 5-ª versão aprovada em dezembro de 2014 For psychiatrists, neurologists, internists and family physicians. ***Information for patients*** Cartão informativo para o doente – 1.ª versão aprovada em dezembro de 2014
Vibativ (telavancin)	***Information for physicians*** Guia para profissionais de saúde - Informação de segurança importante – 1.ª versão aprovada em outubro de 2014 For all potential prescribers.

Educational Materials published on the Infarmed website
(December 2014 to February 2015)

Medicinal product	Click on the links (in Portuguese)
Vimizim (elosulfase alfa)	***Information for healthcare professionals*** Instruções de posologia e administração e outra informação de segurança – 1.ª versão aprovada em outubro de 2014
Xalkori (crizotinib)	***Information for healthcare professionals*** Material educacional para o profissional de saúde – 3.ª versão aprovada em julho de 2014 For respiratory medicine specialists and oncologists who treat luung cancer and for hospital pharmacists ***Information for patients*** Material educacional para o doente – 3.ª versão aprovada em julho de 2014
Xarelto (Rivaroxabano)	***Information for physicians*** Guia do Prescritor – 4.ª versão aprovada em agosto de 2014 For cardiologists, internists, neurologists, family physicians, immunohaemotherapy specialists, vascular and general surgeons.
Ziagen (abacavir)	***Information for physicians*** Informação de segurança: reações de hipersensibilidade graves associadas à utilização de Abacavir – 2.ª versão aprovada em novembro de 2014 For physicians who treat HIV/AIDS patients, as well as for corresponding patient associations.

Compiled by Magda Pedro

Communications to Healthcare Professionals
(December 2014 to February 2015)

Medicinal product (ICD)	Click on the topic for details (in Portuguese)
Aceclofenac	New contraindications and warnings in vascular diseases
Cellcept (mycophenolate mofetil)	Risk of hypogammaglobulinaemia and bronchiectasia
Eligard (*depot* injection of leuprorelin acetate)	Lack of efficacy due to incorrect reconstitution and administration procedure
Imnovid (pomalidomide)	Pregnancy Prevention Programme
Increlex (mecasermin, human recombinant IGF-1)	Resolution of 2013 stockout
INOmax (nitric oxide)	Premature interruption of gas administration in some bottles on account of valve failure
Lentocilin (penicillin)	Market stockout of Lentocilin S 1200, Lentocilin S 2400 and Lentocilin 6.3.3.
Procoralan (ivabradine chlorhydrate)	New contraindications and recommendations to minimize the risk of cardiovascular events and severe bradycardia
Rapiscan (regadenosone)	Minimization of the risk of cerebral vascular accident and prolongation of seizures induced by Rapiscan after administration of aminophyllin
Tecfidera (dimethyl fumarate)	Occurrence of a case of Progressive Multifocal Leukoencephalopathy (PML) in a patient with severe, prolonged lymphopoenia
Valproate: sodium valproate, valproic acid and semisodium valproate	Risks from exposure during pregnancy (click here too)

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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