boletim de FARMACOVIGILÂNCIA

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

VOLUME 19
NUMBER 2
2ND QUARTER 2015

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From the Editor

Pharmacovigilance is an ever ongoing process even for medicines that have been around for a long time. An example of novel safety aspects to be considered when using two "classics": codeine (including in cough preparations), hydroxyzine and ibuprofen.

More in this quarter's issue: fingolimod and progressive multifocal leucoencephalopathy, medicines for hepatitis C, amiodarone and risk of dysrhythmia, latanoprost and eye irritation, interferons and pulmonary arterial hypertension.

Finally, two highlights on ADRs in recent literature, and the usual sections of published educational materials and communications to health professionals, including links for further details.

Infarmed Safety Alerts page:

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

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ISSN:
0873-7118

Codeine
New contraindications

Quick Read
Codeine is now contraindicated in children younger than 12 years and in women who are breastfeeding. Also contraindicated in adolescents with respiratory problems.

Codeine is used not only as a pain killer but also for the symptomatic treatment of acute irritative/dry cough, acute and chronic bronchitis, influenza, and other inflammatory conditions of the airways of an allergic or infectious nature.

Codeine's effects result from its **conversion into morphine** which, in **children** aged less than 12 years, is **variable and unpredictable**, putting these patients at particular risk.

In April 2014, **EMA** initiated a safety review of medicines containing codeine for the treatment of cough and cold in children (less than 18 years), following a previous review within the scope of its use as an analgesic.[1]

In Portugal, two such medicinal products are available in the market: Codipront® and Toseína®. The above safety review was concluded in March 2015, and recommendations were issued in order to keep a favourable benefit/risk profile for these medicinal products:

- Contraindication in children younger than 12 years, in ultrafast CYP2D6 metabolizers, and in breastfeeding women.
- Not to be used in children between 12 and 18 years with respiratory problems.
- Child-proof packaging for oral liquid formulations in order to prevent accidental ingestion.

Leonor Chambel

[1] Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeinecontaining_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f

Hydroxyzine (Atarax®)
New restrictions of use

Quick Read

Before prescribing consider:
– minimum effective dose and dose limits as per patient weight
– higher vulnerability of the elderly
– risk factors for QT interval prolongation
– is patient concomitantly taking a hypokalaemic agent or a CYP3A4/5 inhibitor, such as erythromycin, clarithromycin, diltiazem, an imidazole antifungal, or a protease inhibitor antiviral?

In Portugal, hydroxyzine (Atarax®, syrup and tablets) is indicated in the treatment of anxiety in adults and of pruritus both in adults and children.

EMA started in May 2014 a safety review upon identification of a possible risk of adverse cardiac effects. The review is now concluded and confirms a possible association with **QT interval prolongation and torsades de pointes**, especially in **patients with risk factors**. This effect is related to blockage of certain types of cardiac channels, such as hERG.

The SmPCs and PILs are going to be updated with recommendations and warnings about the use of hydroxyzine in patients with cardiological risk factors. To keep the benefits from hydroxyzine higher than its risks, **EMA** and Infarmed recommend:

- Use the minimum effective dose for the shortest time possible. The dose in adults and in children with a body weight over 40 kg **should not exceed 100 mg daily**. In children weighing up to 40 kg, the maximum dose should not exceed **2 mg/kg/day**.
- Use in the **elderly** is not recommended, since in this age group the drug is slowly eliminated and there is greater vulnerability to anticholinergic effects and other adverse reactions. If used, the dose of hydroxyzine **should not exceed 50 mg per day**.
- It is **contraindicated** in patients with **prolonged QT** or with known risk thereof, with **cardiovascular disease, significant electrolyte imbalance, family history of sudden cardiac death, bradycardia**, or concomitant use of **medicines** which prolong the QT interval and/or may cause torsades de pointes.
- **Caution** should be exerted in patients with **bradycardia** and in patients being treated with medicines that may induce **hypokalaemia** or that are potent **inhibitors of the enzyme alcohol dehydrogenase* or of CYP3A4/5****.

Sílvia Duarte

* Examples of **alcohol dehydrogenase inhibitors**: fomepizole (used as an antidote for methanol and ethylene glycol poisoning) [Brent J et al, 2001; Brent J, 2009], bismuth [Jin L et al, 2004].

** Examples of **CYP3A4/5 inhibitors**: erythromycin, clarithromycin, diltiazem, imidazole antifungals such as itraconazole and ketoconazole, protease inhibitor antivirals such as indinavir, ritonavir, nelfinavir and saquinavir [Katzung BG ed. Basic & Clinical Pharmacology 8th ed, 2001].

Ibuprofen and Dexibuprofen
New safety recommendations

Quick Read
Avoid using high doses of ibuprofen/dexibuprofen in the context of cardiovascular conditions / risk factors.

In June 2014 **EMA** started a safety review of medicinal products containing ibuprofen and dexibuprofen, after the publication of a metaanalysis suggesting that the cardiovascular risk of **high doses of ibuprofen (2,400 mg per day)** could be similar to that of the NSAIDs diclofenac and COX-2 inhibitors.[1]

The review is now concluded and has confirmed the possibility of association with a **small increase in the risk of myocardial infarction and stroke**. The effect of treatment duration is meanwhile not known.

Ibuprofen may moreover interact with low doses of acetylsalicylic acid (ASA) possibly **reducing its antiaggregating effects**, since ibuprofen may competitively inhibit the action of ASA on platelet aggregation. The occasional use of ibuprofen however, does not seem to have a significant effect on platelets.

Although there are no data available on the cardiovascular risk of **dexibuprofen,** it is estimated that the use of doses of **1,200 mg per day** or more may be associated with the same level of risk ascribed to ibuprofen in high doses.

The **SmPCs** and **PILs** of ibuprofen and dexibuprofen containing products will be updated with the new safety recommendations. **EMA** and Infarmed recommend:

- High doses of ibuprofen should be avoided in patients with cardiovascular problems, non-controlled arterial hypertension, congestive heart failure, ischaemic cardiopathy, peripheral arterial disease and cerebrovascular disease.
- The use of high doses of ibuprofen should be adequately pondered in patients with cardiovascular risk factors, such as arterial hypertension, hyperlipidaemia, diabetes mellitus and smoking.

Sílvia Duarte

[1] *Bhala N et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79.*

Fingolimod (Gilenya®)
First case of PML

Quick Read

The first case of progressive multifocal leucoencephalopathy (PML) has been reported in a patient on fingolimod who had not been previously treated with natalizumab (Tysabri®) or any other immunosuppressant.

Fingolimod is indicated as a unique disease modifying agent for adults with very active exacerbation-remission multiple sclerosis with:

- high disease activity in spite of treatment with at least one disease modifying therapy;
- very rapid progression defined as two or more incapacitating flares within one year or one or more MRI gadolinium-enhanced lesion, or a significant increase in the load of T2 lesions comparatively to a recent previous MRI study.

PML (progressive multifocal leucoencephalopathy) is a rare and serious cerebral condition involving the progressive appearance of white matter (leuco) lesions in multiple locations (multifocal) and causing incapacity and high mortality. It is caused by **JC (John Cunningham) virus reactivation**. This virus is frequently found in the general population but causes PML only **when the immune system is weakened**. PML may present with features similar to multiple sclerosis; both involve demyelinization.

PML has been diagnosed in a middle-aged man with multiple sclerosis who was receiving therapy with fingolimod. He had been on beta interferon for 10 months until he had started fingolimod 0.5 mg daily almost five years before the diagnosis of PML.

In a routine follow-up MRI in early 2015 lesions were detected which were compatible with a case of PML. The patient had no signs or symptoms of this condition. Treatment was discontinued and the diagnosis confirmed by a positive PCR for JC virus in a sample of cerebrospinal fluid.

Evidence regarding the risk of PML and the need for further guidance on its management is currently being assessed and any developments will be promptly communicated.

Margarida Guimarães

Medicines for Hepatitis C and Amiodarone
Risk of cardiac arrhythmia

Quick Read

Given the risk of serious bradyarrhythmia, in patients already on Harvoni®, Sovaldi® and/or Daklinza®, amiodarone should only be introduced under close surveillance and monitoring and only if there is no other alternative.

Following a **PRAC** assessment of serious cases of arrhythmia associated with the use of medicinal products for chronic hepatitis C, namely sofosbuvir (Sovaldi®), daclatasvir (Daklinza®) or sofosbuvir+ledispavir (Harvoni®), particularly in patients with heart disease being treated with bradycardic agents, **EMA** confirmed a **risk of serious bradycardia or heart block** in patients medicated with amiodarone.

The cases of serious bradycardia or heart block occurred in patients on amiodarone and Harvoni® or amiodarone and a combination of Sovaldi® and Daklinza®. Of the eight cases reviewed until April 2015, one resulted in fatal cardiac arrest and two required pacemaker insertion. The relation between these events and the above-mentioned medicines was deemed probable.

Given that the **interaction mechanism** with amiodarone remains **unknown,** the **MA** holders should ensure the planning of non-clinical studies to investigate potential pharmacodynamic and pharmacokinetic effects.

The following is recommended for risk minimization:

- Therapy with amiodarone should only be started in patients being treated with Harvoni® or Sovaldi® and/or Daklinza® when other antiarrhytmic agents are contraindicated or not tolerated.
- The patients who do have to receive amiodarone should be monitored, especially during the first weeks of treatment. Patients at greater risk of **bradyarrhythmia** should be **monitored in hospital for the first 48 hours**.
- Given that amiodarone's half-life is long, patients who have discontinued treatment with amiodarone should be **monitored for a few months after the beginning of treatment** with the above hepatitis C medicines.
- Patients who take hepatitis C medicines and amiodarone should be informed about the symptoms of bradycardia and heart block and advised to urgently seek medical help in case they present with them.

The Portuguese versions of the texts to be implemented in the **SmPCs** and **PILs** will be available at Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Márcia Silva

Xalatan® (latanoprost)
Eye irritation

Quick Read

The new Xalatan formulation has been associated with cases of eye irritation. However, no serious cases or lack of efficacy have been reported.

Recently a significant increase in the number of cases of adverse eye reactions, particularly irritation, has been detected following the launch of the **new** Xalatan® **formulation** in the UK and Germany.

Literature data support the explanation offered by the **MA** holder: these cases may result from the new formulation's lower pH, though other factors cannot be excluded.[1]

Though there is **no** evidence of an increase in the number of reports of **serious cases** nor of l**ack of efficacy**, it has been considered that the patients should be informed about how to proceed in case eye irritation supervenes. Xalatan's **PIL** is to be updated with a warning for the patients to seek health professional help should they have serious eye irritation with tearful eyes (which may increase the medicine's elimination rate), or should they be considering suspending the treatment.

The text to be implemented in the **PIL** is available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp&mid=WC0b01ac0580727d1c

Monitoring of this issue is on-going.

Sílvia Duarte

[1] *Coles WH, PA Jaros. Dynamics of ocular pH. British Journal of Ophthalmology, 1984: 549-552.*

Alpha and Beta Interferons
Risk of pulmonary arterial hypertension

Quick Read

A causal link between alpha and beta interferons and the development of pulmonary arterial hypertension cannot be excluded. Pulmonary arterial hypertension is now a listed ADR for these medicines.

The French medicines agency detected in 2014 a safety signal concerning a possible association between alpha and beta interferons and pulmonary arterial hypertension. This was based mainly on spontaneous **ADR** reports received in France until August 2013, most of which were included in a retrospective analysis undertaken by the French pulmonary hypertension reference centre.

PRAC recommended an in-depth review be carried out of the data from the periodical safety update reports (PSURs) and from the European Eudravigilance database, and to include the Savale et al study,[1] together with other published clinical and non-clinical data. From this assessment it has been concluded that a **causal relationship cannot be excluded** between the use of alpha and beta interferons and the development of pulmonary arterial hypertension, a rare but serious occurrence.

PRAC consequently recommended that the holders of **MA** for alpha or beta interferons submit a request to change their **SmPCs** and **PILs** to include the adverse reaction "pulmonary arterial hypertension" in sections 4.8 and 4, respectively. The Portuguese versions of the texts to be implemented in the **SmPCs** and **PILs** are available in the **EMA** website at

PRAC recommendations on signals for update of the product information adopted at the 7-10 April 2015 PRAC.

Magda Pedro

[1] *Savale L et al. Pulmonary arterial hypertension in patients treated with interferon. Eur Respir J. 2014 Oct 16.*

Use of off-label and unlicensed medicinal products is common in hospitalized paediatric patients

This extensive MedLine review (1994-2012) undertaken by a Portuguese group shows that the prescription of off-label and unlicensed medicines is common practice worldwide, especially for pre-term newborns. Off-label prescription, which is often essential for dose modification, can reach up to 70.6% in some studies, whereas the use of unlicensed medicines, usually for formulation modification, can be as high as 47.9%.

Magalhães J et al. Eur J Clin Pharm 2015; 71 (1): 1-13.

Varenicline: risk of the more serious neuropsychiatric adverse effects is not increased

From this metaanalysis including 29 randomized controlled studies, evidence emerged that reinforced the already known profile of neuropsychiatric collateral effects along the lines of sleep disorders, such as insomnia and abnormal dreams. However, there was no increased risk of suicide, attempted suicide, suicidal ideation, depression, or death.

BMJ 2015;350:h1109

Educational Materials published on the Infarmed website
(March to May 2015)

Medicinal product	Click on the links (in Portuguese)
Arava (leflunomide)	***Information for physicians*** Informação de segurança – 2.ª versão aprovada em março de 2015 For rheumatologists. ***Information for patients*** Informação para o doente – 2.ª versão aprovada em março de 2015
Azzalure (botulinum toxin A)	***Information for physicians*** Informação segundo o Plano de Gestão do Risco Europeu – 2.ª versão aprovada em março de 2015 For physicians of various specialities, mainly dermatologists and plastic surgeons. ***Information for consumers*** Linhas glabelares – Tratamento com Azzalure: Resposta a algumas das suas perguntas – 2.ª versão aprovada em março de 2015
Cimzia (certolizumab pegol)	***Information for physicians*** Guia do prescritor – 4.ª versão aprovada em março de 2015 For rheumatologists and internists. ***Information for patients*** Cartão de alerta – 4.ª versão aprovada em março de 2015
Lucentis (ranibizumab)	***Information for physicians*** Guia para a gestão dos riscos associados às injeções intravítreas – 2.ª versão aprovada em outubro de 2014 For ophthalmologists. ***Information for patients*** Guia para o tratamento – perda de visão devida a edema macular secundário a oclusão da veia retiniana – 3.ª versão aprovada em outubro de 2014 Guia para o tratamento – perda de visão devida a neovascularização coroideia secundária a miopia patológica – 2.ª versão aprovada em outubro de 2014 Guia para o tratamento – perda de visão devido a degenerescência macular relacionada com a idade neovascular (húmida) – 4.ª versão aprovada em outubro de 2014 Guia para o tratamento – perda de visão devida a edema macular diabético – 4.ª versão aprovada em outubro de 2014

Educational Materials published on the Infarmed website
(March to May 2015)

Medicinal product	Click on the links (in Portuguese)
Metanor (flupirtine)	***Information for physicians*** Informação de segurança importante – 1.ª versão aprovada em março de 2015 For family medicine, internal medicine, orthopaedic surgery and rheumatology specialists. ***Information for patients*** Informação importante – 1.ª versão aprovada em março de 2015
Multaq (dronedarone)	***Information for physicians*** Cartão de Informação Multaq – 1.ª versão aprovada em fevereiro de 2015 Lista de Verificação do prescritor – 1.ª versão aprovada em fevereiro de 2015
RoActemra (tocilizumab)	***Information for healthcare professionals*** Brochura relativa à indicação terapêutica artrite reumatoide – 6.ª versão aprovada em janeiro de 2015 For doctors and nurses who may prescribe/administer RoActemra. ***Information for patients*** Brochura – 2.ª versão aprovada em janeiro de 2015 Cartão de alerta do doente com artrite reumatoide (SC e IV) – 2.ª versão aprovada em janeiro de 2015 Cartão de alerta do doente com artrite reumatoide, artrite idiopática juvenil sistémica ou artrite idiopática juvenil poliarticular (IV) – 5.ª versão aprovada em janeiro de 2015 Materials to be handed out by healthcare professionals to every patient before they start treatment.
Tasigna (nilotinib)	***Information for healthcare professionals*** Brochura – 4.ª versão aprovada em fevereiro de 2015 For haematologists and all the heads of hospital pharmaceutical services treating patients with chronic myeloid leukaemia. ***Information for patients*** Brochura – 3.ª versão aprovada em fevereiro de 2015

Educational Materials published on the Infarmed website
(March to May 2015)

Medicinal product	Click on the links (in Portuguese)
Toctino (alitretinoin)	***Information for healthcare professionals*** Carta para o médico – 1.ª versão aprovada em abril de 2013 Carta para o farmacêutico – 1.ª versão aprovada em abril de 2013 Guia para médicos sobre a prescrição de Toctino – 1.ª versão aprovada em abril de 2013 Lista para a verificação da prescrição – 1.ª versão aprovada em abril de 2013 ***Information for patients*** Brochura informativa – 1.ª versão aprovada em abril de 2013 Brochura informativa sobre a contraceção – 1.ª versão aprovada em abril de 2013 Consentimento informado para as doentes do sexo feminino – 1.ª versão aprovada em abril de 2013
Valproate (sodium valproate, valproic acid and semisodium valproate)	***Information for physicians*** Guia para o prescritor – 1.ª versão aprovada em fevereiro de 2015 Formulário de comunicação de informação do risco – 1.ª versão aprovada em fevereiro de 2015 For prescribing specialists in neurology, psychiatry and family medicine. ***Information for patients*** Guia de informação – 1.ª versão aprovada em fevereiro de 2015
Vasokinox (nitric oxide)	***Information for healthcare professionals*** Guia de bolso – 1.ª versão aprovada em outubro de 2014
Victrelis (boceprevir)	***Information for physicians*** Informação de segurança - 2ª versão aprovada em junho de 2014 For doctors who treat hepatitis C patients and who are specialists in internal medicine, gastroenterology and infectious diseases.

Compiled by Magda Pedro

Communications to Healthcare Professionals
(March to May 2015)

Medicinal product	Click on the links (in Portuguese)
Atarax (hydroxyzine)	New restrictions to minimize the known risk of QT interval prolongation
Gilenya (fingolimod)	First case of progressive multifocal leucoencephalopathy (PML) in a patient with multiple sclerosis with no previous immunossupressing treatment
Imnovid (pomalidomide)	Minimization of the risk of serious liver toxicity, interstitial pulmonary disease and heart failure
Lentocilin S 1200, S 2400 and 6.3.3. (penicillin)	Market restocked
Mitomicina-C Kyowa 40 mg injection	Exclusive intravesical route for the administration of units from batch 545ADI01
Xofigo (radium dichloride (223Ra))	Change in NIST Standard Reference Material

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:**

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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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