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From the Editor

Volume 20 years of Pharmacovigilance Bulletin

*Boletim de Farmacovigilância is now in its 20th year disseminating safety Information to health professionals. The Boletim's number 1 issue (available **here**) came out in the first quarter of 1997 when the National Pharmacovigilance System was just taking its initial but firm steps. In that first issue a relatively novel finding, the risk of tendinitis and tendon rupture associated with fluoroquinolones, was discussed. Instructions were given for filling out the Adverse Reaction Form, then a yellow card that only prescribing physicians could use.*

Since 1997, Boletim has reported on several hundreds of active ingredients, adverse reactions and risk management and minimization measures. The bulletin, always in both English and Portuguese language versions and with quarterly periodicity, has evolved from a paper-only, snail-mailed format to the current publication which is totally online and available one click away. It now addresses all the professionals who are somehow involved in prescribing, dispensing or administering medicines.

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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SGLT2 Inhibitors
Risk of ketoacidosis

Quick Read

Though rare, serious diabetic ketoacidosis can occur with SGLT2 inhibitors. Patients should be informed about risk factors, how to suspect ketoacidosis and what to do.

SGLT2 inhibitors (sodium-glucose cotransporter 2 inhibitors – canagliflozin, dapagliflozin, empagliflozin) are used for the treatment of type 2 diabetes and act by blocking the SGLT2 protein in the kidneys. SGLT2 is involved in the reabsorption of glucose from urine back into the bloodstream. Glucose elimination in urine is thus increased and blood levels of glucose reduced.

Diabetic ketoacidosis occurs when the body cannot use the glucose in blood due to lack of insulin. Fat is then metabolized as an alternative source of energy, which causes ketones to rise. This happens mostly in type 1 diabetes patients, but it can also supervene in type 2 diabetes.

The following can be manifestations of ketoacidosis: *anorexia, unusual tiredness or sleepiness, nausea, vomiting, abdominal pain, respiratory distress, confusion, excessive thirst, sweet breath, sweet or metallic taste in the mouth, or an unusual odour from urine or sweat.*

Following reports of rare but serious cases of diabetic ketoacidosis in patients on SGLT2 inhibitors, **EMA** started a safety review which culminated in the risk minimization recommendations below. It should be noted that in some of the cases reported the medicines were being used off label or as part of a clinical trial in type 1 diabetics.

- Patients should be **informed about**:
  - signs and symptoms of diabetic ketoacidosis and the need to urgently see a doctor.
  - risk factors for ketoacidosis, including conditions in which food is restricted or which may lead to severe dehydration, a sudden drop in insulin levels, or an increase in insulin needs from illness, surgery or excessive alcohol intake.
- In case ketoacidosis is suspected or confirmed, therapy should be **stopped immediately** and should not be restarted unless an alternative cause for ketoacidosis is detected and resolved.
- Treatment should be **temporarily stopped** in patients who have been admitted to hospital for serious illness or to be submitted to major surgery. It can be restarted once the patient has been stabilized.

Reminder: these medicines are authorized for the treatment of type 2 diabetes only.

Marcia Silva

Repaglinide and Clopidogrel
Possible interaction

Quick Read
Clopidogrel can inhibit repaglinide's metabolism in the liver, therefore potentiating its action.

Repaglinide is usually indicated in adults with type 2 diabetes mellitus. Clopidogrel is used for the prevention of atherothrombotic and thromboembolic events.

Tornio et al.[1] have shown that there is significant pharmacokinetic and pharmacodynamic interaction between clopidogrel and repaglinide. The latter is metabolized by cytochrome P450 (CYP)2C8, which in turn is strongly inhibited by clopidogrel's metabolite acyl-β-D-glucuronide.

Following a centralized assessment of the Periodical Update Safety Reports (PSURs) for repaglinide, **EMA's PRAC** concluded indeed for a potential interaction with the active ingredient clopidogrel.

Although repaglinide's benefit-risk ratio remains positive, **EMA** has considered the drug-drug interaction to be of clinical relevance, which is why the information documents regarding both medicines will be updated accordingly.

Margarida Guimarães

[1] *Tornio A, et al. Glucuronidation converts clopidogrel to a strong time-dependent inhibitor of CYP2C8: a phase II metabolite as a perpetrator of drug-drug interactions. Clin Pharmacol Ther. 2014 Oct;96(4):498-507*

Oxybutynin (topical)
Risk of psychiatric disorders

Quick Read

Pyschiatric disorders can rarely occur with the administration of topical oxybutynin. Special caution should be exercised in adults. Oxybutynin is not recommended in children.

Oxybutynin is a competitive antagonist of acetylcholine at pre-ganglionic muscarinic receptor level, which results in bladder smooth muscle relaxation. Oxybutynin in transdermal patches and as a gel (in sachets or dosing device) is indicated for the symptomatic treatment of urge incontinence and/or increased micturition frequency or urgency, which can occur in adult patients with unstable bladder.

During its routine safety activities, **EMA** has detected a safety signal concerning psychiatric manifestations associated with topical administration of oxybutynin. This was based on thirteen cases reported Europe-wide; of those, seven cases included a positive de-challenge and six required hospitalization.

Given the available data, including evidence from clinical trials and biological mechanism plausibility, **EMA** has considered that a causal link between topical oxybutynin and psychiatric disorders cannot be excluded. However, in the particular case of depression, there did not seem to be sufficient evidence to establish a causal relation; **MA** holders are therefore to keep monitoring this possible adverse effect through routine pharmacovigilance activities.

The use of oxybutynin in the **paediatric population** is **not recommended**. Caution should be exerted in the elderly since they can be more sensitive to the effects of centrally-acting anticholinergic agents and pharmacokinetics in their case may be different.

Magda Pedro

Natalizumab (Tysabri®)
Safety review conclusions

Quick Read

Clinical surveillance including MRI assessment and anti-John-Cunningham (JC) virus antibody testing are essential in the follow-up of patients on Tysabri® (natalizumab) for early detection of progressive multifocal leucoencephalopathy (PML) [see also n. 1 of 2010].

Natalizumab is an anti-α4-integrin humanized recombinant antibody indicated in the treatment of adults with multiple sclerosis.

EMA has concluded a safety assessment on Tysabri® (natalizumab) concerning whether new scientific data should prompt revision of the safety information made available to health professionals and patients to minimize the known risk of associated progressive multifocal leucoencephalopathy (PML).

PML is a rare brain infection caused by the John Cunningham virus (JCV) which can lead to serious incapacity and death. In patients being treated with Tysabri® the known risk factors for PML are: presence of anti-JCV antibodies, treatment duration longer than two years, and previous use of immunosuppressants. Patients with those three risk factors are at higher risk of PML.

New data from clinical trials suggest that the level of anti-JCV antibodies (index*) is related to the risk of PML. More specifically, current evidence suggests that the risk of PML is low for index values ≤ 0.9 and increases substantially in patients with an index > 1.5 who have been treated with natalizumab for over two years.

Recent studies also suggest that early diagnosis and treatment of PML, when the condition still at its initial asymptomatic stages, are extremely important to limit brain damage and ensuing incapacity. Asymptomatic cases of PML can be detected by magnetic resonance imaging (MRI). Based on those data, the **PRAC** concluded that more frequent MRI studies should be considered in patients at higher risk for PML.

Natalizumab (Tysabri®)
Safety review conclusions

Infarmed recommends the following to health professionals:

- Data from clinical trials suggest that in patients who have never before used immunosuppressants the level (index) of anti-JCV antibodies is related to the level of risk of PML. The estimated risk** has been updated as shown in table 1:

Duration of treatment Tysabri	No previous use of immunosuppressants				Previous use of immunosuppressants
	No índex value	Index ≤ 0.9	Index > 0.9 and ≤ 1.5	Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	8

Table 1. Estimated risk of PML per 1000 patients, in patients with anti-JCV antibodies

- **Before starting Tysabri®, patients and their caregivers should be advised on the risk of PML.**
- **Before starting** treatment (preferably within the preceding 3 months), a reference **MRI** and **testing for JCV antibodies** should be undertaken, in order to stratify the risk of PML.
- **During** treatment, patients should be periodically monitored for **signs and symptoms** of de novo neurological impairment and, at least **annually**, a brain **MRI** should be undertaken.
- In patients with **increased risk** of PML, MRI studies should be undertaken more frequently (every 3 to 6 months) and abbreviated protocols (FLAIR, T2 and DW) can be considered, since early diagnosis of PML in asymptomatic patients is associated with an improved course of the disease.
- **PML should be considered in the differential diagnosis** of every patient presenting with neurological symptoms and/or brain lesions on MRI. Asymptomatic cases of PML have been detected based on MRI and the presence of JCV DNA in the cerebrospinal fluid.
- **In case PML is suspected**, the MRI protocol should be extended to include T1 images, and JCV DNA should be tested for in the cerebrospinal fluid by using methods such as polymerase chain reaction (PCR). Treatment with Tysabri® should meanwhile be suspended until PML is excluded.
- **In patients with negative test results** testing for JCV antibodies should continue **at 6-month intervals**. Patients with low indices and who have not previously been on immunosuppressants should also be tested every 6 months and when treatment reaches 2 years.
- **After 2 years of treatment**, patients should once more be informed about the risk of PML associated with natalizumab.
- Patients and their caregivers should further be advised to remain vigilant regarding the risk of PML during **the first 6 months after the end of treatment**.

Margarida Guimarães

** The level (index) of anti-JCV antibodies results from the optical density of a sample which is calibrated against a standard assayed with STRATIFY JCV Dx Select ELIS (Plavina et al, 2014).*

*** The PML risk estimate was obtained through the life table method based on 21,696 patients who took part in the STRATIFY-2, TOP, TYGRIS and STRATA trials. PML risk stratification using the anti-JCV antibody index in patients who had not previously used immunosuppressants was obtained from combining the annual global risk with the distribution of antibody index values.*

Bcr-Abl tyrosine-kinase inhibitors
Risk of hepatitis B virus reactivation

Quick Read

Hepatitis B virus reactivation is a known complication in patients on immunosuppressive chemotherapy. It can also occur with exposure to Bcr-Abl tyrosine-kinase inhibitors.

Bcr-Abl tyrosine-kinase inhibitors are the first line therapy for most patients with chronic myeloid leukaemia (CML). Over 90% of CML cases are associated with the Philadelphia chromosome, an oncogene that results from the fusion of the Abelson (Abl) tyrosine-kinase gene in chromosome 9 with the break point cluster (Bcr) gene in chromosome 22. The resulting Bcr-Abl tyrosine-kinase is implicated in the pathophysiology of CML and is selectively inhibited by tyrosine-kinase inhibitors.

Based on evidence from the literature,[1-4] on cases from the European EudraVigilance database and national assessment reviews, the French Medicines Agency (ANSM) raised a safety signal to do with the use of tyrosine-kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib): reactivation of hepatitis B virus. This is a known complication in patients infected with the virus and who are on immunosuppressive chemotherapy. However, the seriousness of some of the cases and the potential for progression to acute hepatic failure or fulminant hepatitis leading to liver transplantation or death further stressed the relevance of this concern.

After reassessing all the available evidence at **EMA** and **MA** Holder level, **PRAC** concluded for an actual risk of hepatitis B virus reactivation in patients on Bcr-Abl tyrosine-kinase inhibitors. The **SmPCs** (sections 4.4 and 4.8) will be updated accordingly: it is recommended that, **before starting treatment**, patients be tested for HBV infection, and an expert on liver diseases and treatment of hepatitis B should be consulted before initiating treatment in patients with a positive serology.

Leonor Chambel

[1] *Kim SG et al. Transplantation proceedings 2014 Apr; 42(3):843-5. doi: 10.1016/j.transproceed.2010.02.038.*

[2] *JP et al. Supportive care in cancer, 2012 Nov; 20(11):2999-3008. doi: 10.1007/s00520-012-1576-7. Epub 2012 Aug 30.*

[3] *Keam B et al. Why, When, and How to Prevent Hepatitis B Virus Reactivation in Cancer Patients Undergoing Chemotherapy, 2011 Oct, J Nat comprehensive, 9:465-477 cancer network*

[4] *Hwang JP et al., Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update, May 2015, ASCO, doi: 10.1200/JCO.2015.61.3745. Epub 2015 May 11.*

Duodopa® via intestinal tube
Risk of intussusception

Quick Read

A permanent intestinal tube for administration of Duodopa® gel may be associated with adverse gut reactions including intussusception and its potential complications.

Duodopa® is a levodopa + carbidopa combination intestinal gel indicated in the treatment of advanced-stage Parkinson's disease with severe motor fluctuations and hyper/dyskinesia. In long-term therapy, the gel needs to be administered with a portable pump directly into the duodenum or the upper jejunum via an intraintestinal tube.

Intussusception is a serious condition in which part of the gut slides into an adjacent segment thus blocking the passage of food or liquids. It can result in infection, necrosis or even intestinal rupture.

Seven cases of intussusception were detected during routine pharmacovigilance in patients using Duodopa®. Intussusception is not mentioned in the **SmPC** but some of the adverse reactions listed, such as **intestinal ischaemia and perforation**, bezoar (aggregates of non-digestible material retained in the gut) and ulceration, can be clinically associated to it.

After assessing all the available data, **EMA** considered that, although there is not sufficient evidence to decide whether there is an increased incidence of intussusception, an association between the use of the intestinal tubes and the development of intussusception is indeed supported. Moreover, **bezoar formation** around the administration tube may act as a starting point for intestinal obstruction or intussusception.

The **SmPC** and **PIL** of Duodopa® will therefore be updated to include the above information regarding intussusception.

Ana Sofia Martins

Hormonal Replacement Therapy*: oestrogen-progestagen combinations; tibolone; Duavive® (bazedoxifen, conjugated oestrogen)

Risk of ovarian cancer

* except pharmaceutical forms for vaginal use

Quick Read

A recent meta-analysis published in The Lancet points to an increased risk of ovarian cancer in association with the use of postmenopausal hormonal replacement therapy (HRT). An actual causal link is not certain, but women on HRT for five years from about 50 years of age may have an excess of one case of ovarian cancer per one thousand users.

These medicinal products are indicated as hormonal replacement therapy for postmenopausal women.

During its routine safety activities, **EMA** came across a recent publication in The Lancet of a meta-analysis on the risk of ovarian cancer with the use of hormones in the menopause[1] The risk of ovarian cancer is already known for these medicines and is listed in the **SmPC**. From the evidence in the above publication **EMA** concluded however, that a change to the **SmPC** was justified. Thus:

In Section 4.4 - Special warnings and precautions for use:

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the Women's Health Initiative (WHI) trial, suggest that the long-term use of combined HRTs may be associated with a similar, or slightly smaller risk. [...]

In section 4.8 – Undesirable effects:

Use of estrogen-only and or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed [...]

Márcia Silva

[1] *Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Lancet. 2015 May 9;385(9980):1835-42. doi: 10.1016/S0140-6736(14)61687-1. Epub 2015 Feb 13.*

Oral contraceptive exposure just before or during pregnancy – not associated with increased risk of major birth defects –

In this prospective observational cohort study, data on oral contraceptive use and major birth defects were collected among 880,694 live births from Danish registries between 1997 and 2011. The possibility of residual confounding and lack of information on folate notwithstanding, no increase in prevalence of major or segmental (e.g., limb) birth defects was seen with oral contraceptive exposure among women either with recent use before pregnancy or use after pregnancy onset.

Brittany MC et al. BMJ 2016;352:h6712.

Benzodiazepine use and dementia – causal association not supported –

Within the integrated healthcare delivery system of Seattle WA (USA), this prospective population-based cohort study set out to determine whether higher cumulative use of benzodiazepines is associated with a higher risk of dementia or more rapid cognitive decline. A screening instrument was administered every two years to screen for dementia and was used to examine cognitive trajectory. Over a mean follow-up of 7.3 years, although the risk of dementia was slightly higher in people with minimal exposure to benzodiazepines, higher benzodiazepine use was not associated with more rapid cognitive decline. According to the authors these results do not support a causal association between benzodiazepine use and dementia.

Gray SL et al. BMJ 2016;352:i90

Educational Materials published on the Infarmed website
(December 2015 to February 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Abstral (fentanyl)	***Information for physicians*** Guia do prescritor – 3.ª versão aprovada em janeiro de 2016 For doctors in pain clinics, palliative care and oncology departments. ***Information for patients*** Guia do doente – 3.ª versão aprovada em janeiro de 2016
Ácido zoledrónico Hospira (zoledronic acid)	***Information for patients*** Cartão de alerta para o doente sobre a osteonecrose da mandíbula - 1ª versão aprovada em janeiro de 2016
Ácido zoledrónico Zentiva (zoledronic acid)	***Information for patients*** Cartão de alerta para o doente sobre a osteonecrose da mandíbula – 1.ª versão aprovada em novembro de 2015
Actiq (fentanyl, tablets with integrated buccal device)	***Information for prescribing physicians*** Guia para o prescritor – 1.ª versão aprovada em fevereiro de 2016 For doctors in (chronic) pain clinics, palliative care and oncology departments. ***IInformation for patients*** Guia para o doente – 1.ª versão aprovada em fevereiro de 2016 Diário de tratamento para o doente – 1.ª versão aprovada em fevereiro de 2016
Cellcept (mycophenolate mofetil)	***Information for healthcare professionals*** Guia para o profissional de saúde – 1.ª versão aprovada em fevereiro de 2016 For doctors in nephrology, urology, gastroenterology, cardiology, surgery, cardiothoracic surgery and general surgery departments of hospitals undertaking transplants in Portugal, and for pharmaceutical directors in those hospitals. For medical directors of nephrology, urology, gastroenterology, cardiology, surgery, cardiothoracic surgery and general surgery, haematology, rheumatology, internal medicine, respiratory medicine, neurology and OB/GYN departments of all other hospitals, to disseminate these educational materials in their departments. Questionário de gravidez de seguimento – 1.ª versão aprovada em fevereiro de 2016 ***Information for patients*** Guia do doente – 1.ª versão aprovada em fevereiro de 2016

Educational Materials published on the Infarmed website
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Medicinal product (DCI)	Click on the links (in Portuguese)
Estmar (desogestrel + ethinylestradiol)	***Information for physicians*** Lista de verificação para os prescritores – 1.ª versão aprovada em dezembro de 2015 For family doctors and gynaecologists. ***Information for patients*** Perguntas e respostas sobre Estmar: Informação atualizada para as doentes – 1.ª versão aprovada em dezembro de 2015 Cartão de informação para a doente – 1.ª versão aprovada em dezembro de 2015
Exelon (rivastigmine)	***Information for patients*** Cartão de memória para o doente – 2.ª versão aprovada em outubro de 2015
Gilenya (fingolimod)	***Information for physicians*** Guia e lista de verificação do médico prescritor – 5.ª versão aprovada em outubro de 2015 Para médicos neurologistas. ***Information for patients*** Cartão de informação para o doente – 5.ª versão aprovada em outubro de 2015
Kanuma (sebelipase alfa)	***Information for healthcare professionals*** Guia para profissionais de saúde – 1.ª versão aprovada em novembro de 2015 For paediatricians, gastroenterologists, internal medicine specialists, endocrinologists, and for nurses who administer this medicine.
Opdivo (nivolumab)	***Information for physicians*** Guia de controlo de reações adversas imunitárias para o médico - 2ª versão aprovada em novembro de 2015 ***Information for patients*** Cartão de alerta do doente – 2.ª versão aprovada em novembro de 2015
Qutenza (capsaicin)	***Information for healthcare professionals*** Guia de administração de Qutenza para profissionais de saúde – 4.ª versão aprovada em outubro de 2015

Educational Materials published on the Infarmed website
(December 2015 to February 2016)

Medicinal product (DCI)	Click on the links (in Portuguese)
Soliris (eculizumab)	***Information for physicians*** Guia do médico para prescrição em doentes com SHUa – 4.ª versão aprovada em novembro de 2015 Guia do médico para prescrição em doentes com HPN – 4ª versão aprovada em novembro de 2015 ***Information for patients*** Brochura informativa do doente (pais cuidadores) com SHUa – 3.ª versão aprovada em novembro de 2015 Brochura informativa do doente (pais cuidadores) com HPN – 4.ª versão aprovada em novembro de 2015
Tiocolquicosido Generis (thiocolchicoside)	***Information for physicians*** Guia de prescrição para o médico - 1ª versão aprovada em outubro de 2015 For family doctors, orthopaedic surgeons, rheumatologists, gynaecologists, rehabilitation, internal and occupational medicine specialists. ***Information for patients*** Cartão do doente – 1.ª versão aprovada em outubro de 2015
Vellofent (fentanyl)	***Information for physicians*** Guia de prescrição para o médico – 1.ª versão aprovada em janeiro de 2016 For prescribing physicians specialized in oncology and radiotherapy, as well as for physicians in pain units (including anaesthetists) and in palliative care. ***Information for patients and caregivers*** Guia de utilização para o doente e para o prestador de cuidados de saúde – 1.ª versão aprovada em janeiro de 2016
Xarelto (rivaroxaban)	***Information for physicians*** Guia do Prescritor – 5.ª versão aprovada em outubro de 2015 For cardiologists, internists, neurologists, family doctors, immunohaematologists, vascular and general surgeons.
Zometa (zoledronic acid)	***Information for patients*** Cartão de alerta para o doente – 2.ª versão aprovada em outubro de 2015

Compiled by Magda Pedro

Communications to Healthcare Professionals
(December 2015 to February 2016)

Medicinal product	Click on topic for details (in Portuguese)
Combodart / Juteo (dutasteride + tamsulosine)	Out of stock
Dancor (nicorandil)	Risk of ulceration and complication progression
Gilenya (fingolimod)	Risks related to effects on the immune system
Humalog (insulin lispro)	Correct use to minimize medication errors
TachoSil (human fibrinogen/ human thrombin)	Minimization of risk of intestinal obstruction
Tarceva (erlotinib)	Restriction of first-line maintenance therapy indication for the treatment of patients whose tumours present an EGFR activating mutation.
Tecfidera (fumarato de dimetilo)	New measures to minimize the risk of PML – additional monitoring and criteria for stopping treatment.
Viekirax (ombitasvir + paritaprevir + ritonavir))	Viekirax, with or without Exviera, is not recommended in Child-Pugh B patients

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:**

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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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