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From the Editor

This quarter you will find various issues with relevance to commonly used medicines, such as bupropion, fluoroquinolones and renin-angiotensin axis modifiers. Read on about adrenalin autoinjectors and emergency contraceptives, as well as other recent safety issues materialized as educational materials and safety communications to healthcare professionals.

Two habitual sections – ADRs in the Literature and Interactions to keep in mind – come back this time as a two-in-one on interactions with the anticoagulant acenocoumarol, felodipine pharmacokinetics and interactions between calcium channel blockers and macrolides.

And remember you can use your web browser to bookmark the Infarmed link for both the latest and previous safety alerts (in Portuguese):

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

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Bupropion
Risk of pancytopoenia?

Quick Read
It is not certain whether there is a risk of pancytopoenia associated with bupropion, but attention is warranted.

During routine signal detection activities a signal of pancytopoenia potentially associated with the use of bupropion was picked up. Bupropion is a selective neuronal nordarenaline and dopamine reuptake inhibitor which is indicated in the treatment of major depressive episodes in adults.

The Pharmacovigilance Risk Assessment Committee (**PRAC**) at **EMA** recommended that a cumulative revision of cases of pancytopoenia and related terms be made, including a literature review and a discussion of a possible mechanism of action irrespective of the labelled indication. The data provided by the **MA** Holder raised some concerns regarding the occurrence of adverse haematopoenic events and more specifically of anaemia, thrombocytopoenia and leucopoenia. Most cases involved young patients, including children, without relevant comorbidities, and in several cases there were alternative explanations for the reported adverse events.

It was considered that the data did not seem to point to a specific risk for patients. However, given the available evidence and safety data, **PRAC** has recommended that the Summaries of Product Characteristics and Patient Information Leaflets be updated to include information about the risk of pancytopoenia.

The Portuguese versions of the texts to be implemented in the **SPCs** and **PILs** can be found here: Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Margarida Guimarães

Fluoroquinolones
Risk of retinal detachment?

Quick Read

Evidence regarding a possible association between fluoroquinolones and retinal detachment seems inconsistent. Special awareness is in the meantime warranted for the occurrence of vision disturbances during or following exposure to this group of antibiotics.

In October 2012, the **PRAC** at **EMA** discussed a case-control study (**Etminan M et al.**) which concluded that there was an increased risk of retinal detachment in association with exposure to fluoroquinolones. This study was considered to be hampered by significant limitations and no specific regulatory measure was taken. Other epidemiological studies on the topic have been published and **EMA** has also conducted an analysis of the ***Network Health Improvement*** database. Studies vary in relation to methods, populations and degree and forms of adjustment for possible confounding factors. On the whole, they show **inconsistent and variable results**.

A population-based, retrospective, cohort study undertaken by **Kuo et al.** has shown a seemingly significant association between fluoroquinolones and risk of retinal detachment. However, the timelines do not support the Etminan study results which point to an acute effect. Analyses conducted by **Fife et al.** on two USA databases, including one attempt at replicating the results of Etminan et al. did not show a risk of the same magnitude. **Others** have not found a significantly increased risk either.

Kapoor et al. used data from the Rochester Epidemiology Project and did not find an increased risk within 90 days of exposure to fluoroquinoones when compared to macrolides and beta-lactams. **Eftekhari et al.** studied the THIN database comparing cohorts of patients who had been prescribed fluoroquinolones or beta-lactams – no increased risk rate was observed 30 and 90 days after exposure. In a cohort study undertaken by **Pasternak et al.** there was no increased risk of retinal detachment associated with the use of fluoroquinolones.

All the above studies have limitations as to their ability do deal with the complexity of ophthalmological confounding factors and retinal detachment risk factors. Moreover, most studies were undertaken using databases which included limited information on confounding factors. The populations under study were heterogeneous. Given the rarity of the occurrence of retinal detachment many studies excluded great risk increases, but confidence intervals were relatively wide; small risk increases cannot therefore be excluded, especially in patients with risk factors.

Since October 2012, new spontaneous cases of retinal detachment with fluoroquinolones have been inserted in the European database Eudravigilance, which may have been motivated my the publication by Etminan et al. and ensuing discussions by the regulatory authorities.

For now, in brief, a causal relation between exposure to fluoroquinolones and retinal detachment cannot be either determined or excluded based on the currently available data. As a precaution, in the meantime, a warning about the possibility of visual disturbances is to be included in the information documents of this group of antibiotics. The **PRAC** has concluded it appropriate to update the corresponding **SPCs** / **PILs** to include the risk of retinal detachment.

The Portuguese versions of the texts to be implemented can be found here:

Recomendações do PRAC decorrentes de avaliação de sinais de segurança.

Margarida Guimarães

Renin-Angiotensin Axis Modifiers
Simultaneous use not recommended

Quick Read

Except in rare and restricted conditions, only one renin-angiotensin axis modifying drug should be used at a time.

The renin-angiotensin hormonal system controls arterial blood pressure and fluid volume in the body. Medicines able to act on this system can do so in three general ways: by antagonizing the angiotensin receptors (ARAs), by inhibiting the angiotensin converting enzyme (ACE inhibitors), or by directly inhibiting renin (e.g., aliskiren). In Portugal, medicines from all three groups are authorized and marketed.

Given the results of some published studies, including a recent metaanalysis of 33 clinical studies involving over 68,000 patients published in the British Medical Journal (**Makani H et al, 2013**), **EMA** has undertaken a safety review to assess the impact of the simultaneous use of various renin-agiotensin axis modifying agents for the treatment of hypertension and congestive heart failure. The risks of hypercalcaemia, arterial blood pressure reduction and renal failure were analyzed for the use of combinations in comparison to the use of a single agent. It was also researched whether combined use was superior to the use of a single agent in terms of global mortality.

Following the above review, **PRAC** recommended that renin-angiotensin axis modifying agents should not be used in simultaneous combination for the treatment of hypertension or congestive heart failure.

In particular, patients with diabetes-associated kidney impairment (**diabetic nephropathy**) should not be given angiotensin receptor antagonists (ARA) and angiotensin-converting enzyme (ACE) inhibitors simultaneously. Whenever this combination is considered to be absolutely necessary, it should be prescribed by a specialist, who should monitor renal function, fluid and electrolyte balance and blood pressure.

Simultaneous use of **aliskiren and an ARA or an ACE inhibitor in patients with renal conditions or with diabetes is contraindicated** on the grounds that this drug combination increases the risk of adverse cardiac, circulatory and renal effects.

The **PRAC's** current conclusions are based on several studies conducted in patients with various heart and circulatory conditions or with type 2 diabetes, in whom the simultaneous use of an ARA and an ACE inhibitor was associated with an increased risk of hyperkalaemia, renal injury or hypertension, when conmpared with the use of each type of medicine separately.

Continued on next page

Renin-Angiotensin Axis Modifiers
Simultaneous use not recommended

Continued from previous page

Furthermore, no evidence of benefit was found with the use of two renin-angiotensin axis modifiers (dual blockade) in patients without heart failure. The benefits from **simultaneously using** those medicines **only** outweigh the risks in a **restricted group of patients with cardiac failure in whom the use of other drugs is not recommended**.

EMA and Infarmed recommend:

- Concomitant therapy with more more than one renin-angiotensin axis modifying agent (dual blockade) is not recommended, especially in patients with diabetic nephropathy.
- Simultaneous use of aliskiren with an ARA or an ACE inhibitor in patients with diabetes mellitus and moderate to severe renal failure (GFR <60 ml/min/1.73 m^2) is contraindicated.
- In case the simultaneous use of more than one of these medicines is absolutely necessary, renal function, fluid and electrolyte balance and blood pressure monitoring should be undertaken by a specialist.
- Dual blockade (concomitant use of candesartan or valsartan) should only be considered in case of intolerance to mineralocorticoid antagonists, in patients with heart failure.

Margarida Guimarães

Adrenaline Autoinjectors
Risk of accidental exposure

Quick Read
Is the absorption profile of adrenaline administered via an autoinjector adequately consistent across all patients? Ongoing review.

Adrenaline (epinephrine) is administered by autoinjector as first aid before emergency medical assistance in individuals at risk or who have had a previous episode of anaphylaxis. The injection of adrenaline helps to rapidly abate the manifestations of anaphylaxis by producing vasoconstriction (and therefore an increase in blood pressure) and bronchodilation.

The UK Medicines Agency has requested that **EMA** undertake a safety review of autoinjectors, after concluding that, although the information that goes along with these medicinal products states that adrenaline is released into the muscle, there does not seem to be robust evidence that this happens in every patient. Depending on individual factors, such as relative skin/muscle thickness, adrenaline may be injected under the skin rather than into muscle tissue, which may result in an unexpected absorption profile.

EMA has set out to review the availabe data on the administration of adrenaline via autoinjectors, as well as on whether the current product information is adequaqtely clear and detailed. The conclusions form this review will be disseminated as soon as they become available.

Emergency contraceptives and body weight

Quick Read

Emergency contraceptives levonorgestrel and ulipristal are still adequate for their indication irrespective of the woman's body weight.

Emergency contraceptives, which work by stopping or delaying ovulation are used to prevent unintended pregnancy following unprotected sexual intercourse or contraceptive failure. Emergency contraceptives containing **levonorgestrel** can be used **up to 72 hours** after unprotected sexual intercourse or contraceptive failure, while **ulipristal acetate** can be used **up to 120 hours** afterwards.

EMA has concluded a review of these emergency contraceptives to assess whether increased bodyweight affects their effectiveness. The **available data** are limited and not sufficiently robust to support with certainty a conclusion of decreased contraceptive effect with increased body weight / body mass index (BMI). Therefore, the Agency's Committee for Medicinal Products for Human Use (CHMP) **recommends** that these emergency contraceptives can continue to be used in women of all weights; they have generally mild side effects, their benefits outweigh their risks and their safety profile remains favourable.

Women should be reminded that emergency contraceptives should be taken as soon as possible following unprotected sexual intercourse, and that they should only be used as an occasional 'rescue' method, not as a regular contraceptive method.

Educational Materials published on the Infarmed website
(June to August 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
Cimzia (certolizumab pegol)	***Information for the prescribing physicians*** Guia do prescritor – 3.ª versão aprovada em abril de 2014 For rheumatology and internal medicine specialists. ***Information for patients*** Cartão de alerta – 3.ª versão aprovada em abril de 2014
Diane 35 (ciproterone + ethinylestradiol)	***Information for physicians*** Lista de verificação para os prescritores – 1.ª versão aprovada em agosto de 2014 For gynaecologists/obstetricians, dermatoogists and family doctors. ***Information for patients*** Cartão de informação – 1.ª versão aprovada em agosto de 2014
Eliquis (apixaban)	***Information for physicians*** Guia do prescritor – 2.ª versão aprovada em janeiro de 2014 For all prescribing physicians, especially cardiologists, neurologists, internal medicine specialists, family doctors and haematologists. ***Information for patients*** Cartão de alerta – 2.ª versão aprovada em janeiro de 2014
Erivedge (vismodegib)	***Information for healthcare professionals*** Brochura – 1.ª versão aprovada em novembro de 2013 Formulário de verificação de aconselhamento – 1.ª versão aprovada em novembro de 2013 ***Information for patients*** Brochura - 1ª versão aprovada em novembro de 2013 Cartão de informação - 1ª versão aprovada em novembro de 2013
Leflunomida Farmoz Leflunomida Pentafarma (leflunomide)	***Information for physicians*** Brochura - 1ª versão aprovada em março de 2014

Educational Materials published on the Infarmed website
(June to August 2014)

Medicinal Product (DCI)	Click on the links (in Portuguese)
MabThera (rituximab)	***Information for healthcare professionals*** Guia para a utilização segura e eficiente do medicamento – 1.ª versão aprovada em abril de 2014 Cartão comparativo – 1.ª versão aprovada em abril de 2014 For haematologists and oncologists, as well as for hospital pharmacists and nurses.
Orphacol (cholic acid)	***Information for physicians*** Informação de segurança importante – 1.ª versão aprovada em junho de 2014 For hepatologists and more specifically paediatric hepatologists.
Pioglitazona Zentiva (pioglitazone)	***Information for physicians*** Guia de prescrição – 1.ª versão aprovada em março de 2014 For family doctors, internists and endocrinologists.
Tasigna (nilotinib)	***Information for healthcare professionals*** Brochura com informação de segurança importante – 3.ª versão aprovada em abril de 2014 For haematologists and for heads of pharmaceutical departments at hospitals treating patients with chronic myeloid leukaemia.
Zometa (zoledronic acid)	***Information for patients*** Material educacional – 1.ª versão aprovada em fevereiro de 2014

Compiled by Magda Pedro

Comunications to Healthcare Professionals
(June to August 2014)

Medicinal Product (DCI)	Click on topic for details (in Portuguese)
Domperidona (Domperidone)	New recommendations to minimize cardiac risk.
Erivedge (vismodegib)	Potential problem with labels: important to read PIL as a precaution to ensure safe use.
Fentanyl (skin patches)	Risk of accidental exposure to skin patches.
Invirase (saquinavir)	Important safety update including indication for an ECG before treatment and approximately 10 days after its start.
MST (morfine)	Change in the name of prolonged-release MST tablets to make dose more explicit.
Pedea (ibuprofen)	Out of stock situation and important information regarding differing concentrations of alternative medicine.
Velcade (bortezomib)	Isolated cases of broken/cracked phials.

Compiled by Catarina Costa

Interactions to keep in mind!
ADRs in the Literature...
Acenocoumarol and drugs with greater risk of "real life" interactions

This study employed a double retrospective data analysis methodology encompassing up to 14 years to analyze the more clinically relevant drug-drug interactions involving acenocoumarol which affected the safety of patients in a Swiss university hospital. A total of twenty-eight drugs were identified as having a **high risk of interaction** with acenocoumarol, namely:

Acetylsalicylic acid
Amiodarone
Celecoxib
Ciprofloxacin
Clarithromycin
Clopidogrel
Diclofenac
Econazole
Escitalopram
Esomeprazole
Etodolac
Fluconazole
Fluvastatin
Fluvoxamine
Ibuprofen
Imatinib
Ketorolac
Leflunomide
Lysine acetylsalicylate
Metronidazole
Miconazole
Omeprazole
Pantoprazole
Paracetamol
Prednisone
Simvastatin
Valproic acid
Voriconazole

The **most frequently** found mechanism (75% of cases) was **pharmacokinetic**. Only 14% of interactions were caused by pharmacodynamic mechanisms (11% non-identified).

Gschwind L et al. Eur J Clin Pharmacol. 2013;69(3):617-27.

Interactions to keep in mind!
ADRs in the Literature...
Felopidine:
A weak cytochrome inhibitor?

This small-scale study on six healthy subjects for seven days concluded that felodipine may be a weak in vivo inhibitor of cytochromes CYP3A and CYP2D6, but is unlikely to act as a significant precipitant of pharmacokinetic drug-drug interactions.

Snyder BD et al. EurJClinPharm 2014;70(9):1115-1122

Interactions to keep in mind!
ADRs in the Literature...
Interactions between calcium channel blockers and clarithromycin, and renal injury

Calcium channel blockers (e.g., amlodipine, felodipine, nifedipine, diltiazem, verapamil) are metabolized by cytochrome P450 3A4. Clarithromycin is an inhibitor of CYP3A4 whereas azithromycin is not. In this population-based retrospective cohort study undertaken in Ontario, Canada, the authors aimed to characterize the risk of acute adverse events within the first 30 days of a new co-prescription of clarithromycin compared with azithromycin in older adults taking a calcium-channel blocker. Concomitant use of calcium channel blockers (especially dihydropyridines) with clarithromycin vs. azithromycin was associated with a small but statistically significantly greater 30-day risk of hospitalization for acute kidney injury. These findings support that cautionn should be exerted when using CYP3A4 inhibitors in patients taking calcium channel blockers.

Gandhi S et al. JAMA. 2013;310(23):2544-2553.

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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