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From the Editor

The use of topical medicines on the skin is often assumed to be relatively straightforward. Practice indicates that unexpected safety problems can sometimes arise from poor interpretation of the instructions of use or poor handling technique of application devices. Spontaneous reporting is in this respect also of great relevance, allowing otherwise unforeseeable safety issues to be identified and minimisation measures devised. In fact, additional safety precautions may become advisable when a significant cluster of cases seems to be pointing to a recurrent pattern of difficulties in the use of a given product. The Boletim illustrates this issue with three articles drawing our attention to possible adverse reactions associated with the use of drugs commonly applied on the skin (capsaicin and calamine) and with a contraceptive whose effectiveness is dependent on the correct use of the corresponding device - a vaginal ring in this case.

The Australian Prescriber has recently published (Aust Prescr 2013;36:13-6) a set of twelve core competencies for safe prescribing. The definition of these competencies bears in mind their possible usefulness in training syllabus elaboration and in prescriber assessment and credentialing systems. The starting point is the assumption that safe prescribing is complex and involves several cognitive and decision making steps throughout four distinct prescription stages: data collection, clinical decision making, communication, and monitoring and review. These four stages have two underlying aspects: knowledge facilitation (especially in clinical pharmacology) and global attributes such as self-reflection.

Emphasis is given similarly to both communicating and monitoring the therapeutic decision and to pondering and deciding which treatment to use. Communication and follow-up are therefore highlighted as central to therapeutic safety.

An adapted version of the summary table of the competencies described is presented overleaf. For more details you can access the following link: http://www.australianprescriber.com/magazine/36/1/13/6.

What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
PIL	Patient Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

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:**
  www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM
- **Postage Paid Card**

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12 core competencies for safe prescribing	
Stages of prescribing	**Core competencies**
1. Information gathering – skill of gathering relevant information to inform selection of treatment	1. Take and/or review medical history. 2. Take and/or review medication history and reconcile this with medical history. 3. Undertake further physical examination/ /investigations where appropriate. 4. Assess adherence to current and past medication and risk factors for non-adherence.
2. Decision making – collaborative decision making with the patient/ / carer; selection of treatment	5. Identify key health and/or medication related issues with the patient, including making or reviewing the diagnosis. 6. Determine how well disease and symptoms are managed/controlled. 7. Determine whether current symptoms are modifiable by symptomatic treatment or disease modifying treatment. 8. Consider ideal therapy (drug and non-drug), taking into account actual and potential contraindications/concerns: drug–patient, drug–disease, drug–drug interactions. 9. Select drug, form, route, dose, frequency, duration of treatment.
3. Communicate decision – safely and effectively communicate treatment decisions to other health professionals and the patient / / carer in both the ambulatory and the inpatient setting	10. Communicate prescribing decision in an ambulatory care setting. 11. Communicate prescribing decision in an inpatient setting.
4. Monitor and review – review therapeutic and adverse impact of treatment	12. Review control of symptoms and signs, adherence, patient's outcomes.

Combined Hormonal Contraceptives: safety review

On request from the French agency, EMA has initiated a review of safety data concerning EU-authorized third and fourth generation combined hormonal contraceptives, which aims to ascertain whether it should be necessary to limit their use to women who cannot take other combined hormonal contraceptives. The request followed other initiatives set in motion by the French agency to reduce the use of third and fourth generation pills and to increase the use of second generation oral contraceptives.

Combined hormonal contraceptives contain two types of hormones: an oestrogen and a progestin. The current review includes **all third and fourth generation** contraceptives including any of the following ingredients for a progestin: **chlormadinone, desogestrel, dienogest, drospirenone, ethonogestrel, gestodene, nomegestrol, norelgestromine, or norgestimate**.

It has been known for years that combined pills entail a very low risk of venous thromboembolism (VTE). Information on the risk of VTE associated with combined oral contraceptives has been constantly monitored, updated and is laid out in the Information Leaflets and SPCs. The risk is dependent both on the amount of oestrogen present and the type of associated progestin. Though low, it is known to be higher with some progestins in comparison with levonorgestrel.

Combined hormonal contraceptives have therefore been subjected to intensive monitoring by national pharmacovigilance systems and up to now there seem to be no reasons for women to stop taking their contraceptive pills. In case of doubt, questions should be taken up with the patient's attending physician.

Catarina Costa

Tredaptive, Pelzont® and Trevaclyn®: suspension recommended

The Committee for Medicinal Products for Human Use (CHMP) at EMA has confirmed the suspension of the Marketing Authorizations of Tredaptive®, Pelzont® and Trevaclyn® (**nicotinic acid + laropiprant**), which had been authorized in Europe for use in combination with a statin when monotherapy with statins is not sufficient. They should only be used in patients who could not take statins.

EMA started a safety review in December 2012 following the data from a trial including over 25,000 patients, whose preliminary results clearly showed that the use of this medicinal product with statins did **not present any additional benefit** in the reduction of the risk of serious cardiovascular events in patients at high risk, although it effectively decreased serum triglycerides and raised HDL levels. The study also demonstrated that the patients on this medicinal product had an **increased incidence of serious adverse reactions**, such as haemorrhage, muscle weakness, infections and diabetes.

Given the above, the CHMP concluded that the benefits do not outweigh the risks associated with these medicines and their MAs should therefore be suspended. In Portugal, only Tredaptive® and Trevaclyn® were being marketed. The corresponding pharmaceutical company recalled them within the whole of the EU in January 2013. Tredaptive®, Pelzont® and Trevaclyn® are no longer available in the market and should not be prescribed further. Patients should not discontinue their treatment without medical indication to do so. They should therefore see their doctor for therapy review. Pharmacists should refer patients to their attending physicians.

Etonogestrel + ethynilestradiol vaginal ring (NuvaRing®): Important information on application and removal

NuvaRing® is indicated for women of childbearing age, its safety and effectiveness having been established for females aged between 18 and 40 years. The vaginal ring received marketing authorization in 2001.

The vaginal ring should be placed on the indicated day of the menstrual cycle and be left in place for three consecutive weeks. Once the **third week is finished**, NuvaRing® should be removed **on the same week day and at approximately the same time** it had initially been placed. For instance, if NuvaRing was applied on a Wednesday at about 10 pm, it should be removed three weeks later also on a Wednesday at about 10 pm.

- During the pause week without the ring, the woman should usually expect her period.
- Once exactly one week without the ring has gone by, a new ring should be placed (again on the same week day and at approximately the same clock time), **even if menstrual bleeding has not stopped yet**.

One of the risks from using this contraceptive ring incorrectly is that of **expulsion**, which can lead to contraceptive failure and/or the appearance of unexpected bleeding. To ensure its effectiveness, the woman should regularly check for the presence of NuvaRing® in situ.

In case the ring is accidentally expelled, there will be no reduction in contraceptive efficacy if it is left outside the vagina **for less than three hours**. The woman should **rinse the ring with cold or tepid** (never hot) water and reinsert it as quickly as possible within three hours at the latest.

Should NuvaRing® remain or be suspected to have remained outside the vagina for **longer than three hours**, its **contraceptive efficacy** may have **diminished**.

The patient should read the product's Information Leaflet and, in case of doubt, talk to her doctor or pharmacist. As an additional measure to minimize the risk of contraceptive failure due to incorrect use, an **alert card** with the above advice will be handed out to patients.

Margarida Guimarães

Capsaicin patch (Qutenza®): risk of serious burns

Capsaicin is used as a local anaesthetic in the treatment of neuralgia. The skin patch Qutenza® is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults, in isolation or in association with other pain medication. It is estimated that since it was first introduced in the market in 2009, this product will have been used by over 15,000 patients worldwide.

During routine signal detection activities based on cases extracted from EudraVigilance (the European database of adverse drug reactions), a potential risk of serious burns has been identified. The Pharmacovigilance Risk Assessment Committee (PRAC) at EMA, following a review of the product's safety and efficacy data, has concluded that the benefit-risk ratio of Qutenza® (capsaicin) remains positive for the approved indications. The medicinal product's information is going to be altered in order to include the risk of serious burns and to advise health professionals regarding **protection** from accidental exposure with mask, goggles and gloves.

Margarida Guimarães

Caladryl® (diphenidramine + calamine + camphor skin lotion): for external use only

Several cases of incorrect oral administration of this product have been detected, both in children and in adults. When prescribing or dispensing Caladryl®, it is important to reinforce advice regarding correct administration by pointing out that the product should be applied directly on the affected skin area and must not be drunk or swallowed.

See also Boletim n. 1, 2011, online at:

http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PHARMACOVIGILANCE_BULLETIN/2011/farm_%201trim_ingles_2011.pdf

Cristina Mousinho

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ADRs in the literature...

Selective Serotonin Reuptake Inhibitors (SSRI) possibly not associated with perinatal mortality

Use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has been associated with congenital anomalies, neonatal withdrawal syndrome, and persistent pulmonary hypertension of the newborn. This population-based cohort study from all Nordic countries from 1996 to 2007 aimed to find out any effects on perinatal mortality which could have so far gone unnoticed. From an analysis of the pregnancies of a total of 29,228 mothers who had filled prescriptions for SSRIs during pregnancy, it initially seemed that the exposed women had relatively higher rates of stillbirth and postneonatal death. However, further analysis and calculation of adjusted odds ratios eventually showed that no significant association could be found between use of SSRIs during pregnancy and risk of stillbirth, neonatal mortality, or postneonatal mortality. In any case, SSRI prescription during pregnancy should always take into account **other potential perinatal adverse reaction risks** versus the risks associated with background maternal mental illness.

Stephansson O et al. JAMA. 2013;309(1):48-54

ADRs in the literature...

Concurrent use of antihypertensives with non-steroidal anti-inflammatory drugs and risk of acute kidney injury

In this retrospective cohort study using nested case-control analysis of data from the UK Clinical Practice Research Datalink corresponding to almost half a million users of antihypertensive drugs it was concluded that, in general terms, the use of anti-hypertensive therapy with a diuretic, an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) with addition of a non-steroidal anti-inflammatory drug (NSAID) was not associated with an increased rate of acute kidney injury. However, **an NSAID together with double therapy** with a diuretic and either an ACE inhibitor or an ARB was associated with increased renal risk, which was greatest at the start of treatment (first 30 days).

Lapi F et al. BMJ 2013;346:e8525

ADRs in the literature...

Safe use of orally administered cytotoxic agents

The oral route is increasingly used to administer cytotoxic therapy (e.g., capecitabine, methotrexate) for cancer and other conditions. Oral cytotoxic agents carry the same risk of medication errors as parenteral therapy. It is therefore essential that health professionals involved in providing oral cytotoxic therapies understand how they are used, what adverse reactions can potentially occur and how to minimize medication errors.

Carrington C. Aust Prescr 2013;36:9–12

ADRs in the literature...

Lithium: toxicity profile

A systematic review and meta-analysis of randomized controlled trials and observational studies was undertaken to characterize the profile of lithium, a drug widely used with effectiveness in the treatment of mood disorders. Main conclusions:

- Lithium is associated with increased risk of **reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain**. Because of the consistent finding of a high prevalence of **hyperparathyroidism**, the authors recommend that **calcium concentrations be checked** before and during treatment.
- There is little evidence for a clinically significant reduction in renal function in most patients, and the **risk of end-stage renal failure is low**.
- The risk of congenital malformations is uncertain, therefore the benefit-risk ratio should be carefully taken into account whenever considering withdrawing lithium during **pregnancy**.

McKnight RF et al. Lancet 2012;379(9817):721-8.

Interactions to keep in mind!

Patients treated with cytotoxic antineoplastic agents

Interactions in general

- **With enzyme inducers or inhibitors**:
  - risk of decreased efficacy or increased adverse reactions
- With medicines associated with increased risk of adverse **haematological** reactions in general, **thrombosis** or **delayed wound healing**:
  - risk of potentiation of these ADRs
- With vitamin K antagonist **anticoagulants**:
  - risk of raising INR (prefer heparin if possible)
- With other **immunosuppressants**:
  - increased risk of infection and of lymphoid proliferation
- With **vaccines**:
  - risk of decreased immune response and vaccine effectiveness
  - risk of invasive disease in the case of live attenuated vaccines
- With **antiepileptic** agents:
  - risk of decreased anti-seizure or antineoplastic efficacy
- With **dexamethasone**:
  - risk of potentiating the adverse reactions of cytotoxic and antiemetic agents, especially hypokalaemia, salt and water retention, neuropsychiatric disorders
- The absorption of medicines via the **oral route** may be altered by the effects of cytotoxic agents in the gut mucosa.

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http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PHARMACOVIGILANCE_BULLETIN/ONLINE_INDEX

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