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Levetiracetam (Keppra®)
Prescribing and administering the oral solution

Quick Read
The labelling and packaging of levetiracetam oral solution has been optimized with self-explanatory colour-coded graphics. The aim is to minimize the risk of accidental overdose, especially in children, through the use of the wrong syringe or by making a measurement mistake.

Levetiracetam is used for the treatment of epilepsy in children and adults. Its mechanism of action is not completely known but in vitro studies point to actions on the intraneuronal levels of Ca2+, on GABA, glycine and on proteins of the synaptic vesicle.

EMA's PRAC has assessed a safety signal (suspected safety problem) in relation to cases of accidental overdose of Keppra® oral solution. Most cases occurred in children between 6 months and 11 years of age due to the use of the wrong syringe or due to incorrect dose measurement.

In the paediatric age brackets the doses of this medicine need to be adjusted to age and body weight, which makes the oral solution its most widely used pharmaceutical form in children younger than 6 years. In Portugal, Keppra 100 mg/ml oral solution is marketed in 300-ml bottles packed together with a **10-ml syringe**.

To avoid medication errors and minimize the risk of overdose, measures have been put in place to promote the correct use of the graduated measurement syringe:

– The various presentations are to be differentiated by means of a colour scheme for labelling and packaging, which will clearly show the volume of the bottle, the volume of the graduated syringe and the age bracket they are intended for:

– **Recommendations:**:

- **Physicians should prescribe levetiracetam oral solution in mg and with the corresponding ml, based on the patient's age;**
- Patients and/or their caregivers should be educated on how to correctly measure the oral solution, as well as on possible signs of overdose (**sleepiness, agitation, difficulty breathing, coma**);
- Patients and/or their caregivers should be made aware of the importance of only using the **syringe that comes inside the package**. The empty bottle and the used syringe should be **handed in to the pharmacy** for elimination.

Additionally, the labelling and packaging of **generic products containing levetiracetam** oral solution will also be updated with colour coding and clear instructions.

Magda Pedro

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Vitamin K Antagonists and Anti-Hepatitis C Antivirals
Interaction

Quick Read
Boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, ritonavir, simeprevir, sofosbuvir, velpatasvir – a drug-drug interaction can occur between these direct action antiviral agents (DAAVs) used in the treatment of hepatitis C and vitamin K antagonists (such as warfarin) leading to INR decrease.

In analytical terms, the anticoagulant effect of vitamin K antagonists such as warfarin is reflected on a prolonged/raised INR (International Normalized Ratio).

Concomitant use of direct action antiviral agents used in the treatment of hepatitis C (DAAVs) and vitamin K antagonists can lead to INR reduction. PRAC assessed the available data from reported cases and the biological plausibility of the INR changes. The SmPCs/PILs of DAAVs are to be updated with a recommendation that, although changes in the pharmacokinetics of warfarin are not expected in their presence, the **INR should be closely monitored** due to variation in liver function during therapy.

Margarida Guimarães

Tigecycline (Tygacil®)
Risk of hypofibrinogenaemia

Quick Read
Tigecycline can be associated with a reduction in blood serum levels of fibrinogen.

Tigecycline is a tetracycline that is indicated in the treatment of complicated intraabdominal infections and of skin and soft tissue infections (excluding those in the diabetic foot), when other antibiotics are not adequate and after taking into consideration the official recommendations regarding the appropriate use of antimicrobials.

In a study assessing the impact of tigecycline on coagulation in patients with severe infections, of the twenty patients treated, nineteen showed significantly reduced levels of fibrinogen in comparison with the control group treated with cefoperazone-sulbactam.[1] This decrease was more pronounced in the patients who received higher doses of tigecycline.

Based on these and other cases in the literature[1–7], as well as on the European adverse reaction database EudraVigilance, EMA raised a safety signal. Most EudraVigilance cases describe decreased levels of fibrinogen, with or without changes in other coagulation parameters, with a temporal association with tigecycline. In several of those cases, the levels of fibrinogen increased again after the antibiotic had been discontinued.

The following change to the SmPC has been accordingly recommended:

> 4.8 Undesirable effects
> Unknown frequency (cannot be calculated from the available data): hypofibrinogenaemia

Leonor Chambel

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Metformin
and moderately reduced renal function

Quick Read
Patients with an indication for treatment with metformin may benefit from this drug including when their renal function is only moderately impaired (GFR = 30-59 ml/min). Their renal function should be monitored before therapy is started and then annually.

The oral antidiabetic biguanide metformin is excreted by the kidneys. Patients with impaired renal function are at greater risk of developing lactic acidosis, a rare but potentially fatal complication resulting from the accumulation of metformin as a result of elimination half-life prolongation.

The information included in the SmPCs of the medicinal products containing metformin regarding its use in patients with reduced renal function was not harmonized throughout Europe. A review was recently undertaken which included the literature, clinical data, epidemiological studies and clinical guidelines[1-10].

It was concluded that the population with moderately reduced kidney function (Glomerular Filtration Rate (GFR) = 30-59 ml/min) can benefit from the use of metformin in the treatment of type 2 diabetes mellitus. **Meanwhile, the contraindication in patients with GFR < 30 ml/min still applies**.

The SmPCs of metformin are to be updated to include the indication in patients with moderately reduced renal function. In these patients lower doses should be considered and the GFR should be assessed before therapy is started and then annually.

Márcia Silva

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What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorisation
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PIL	Patient Information Leaflet
SmPC	Summary of the Product's Characteristics

Educational Materials published on the Infarmed website

Medicinal product (DCI)	Click on the links (in Portuguese)
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Imlygic (talimogene laherparepvec)	***Information for healthcare professionals*** Guia para o médico – 1.ª versão aprovada em julho de 2016 ***Information for patients*** Guia para o doente/prestadores de cuidados de saúde e contactos próximos – 1.ª versão aprovada em julho de 2016 Cartão de Alerta para o Doente – 1.ª versão aprovada em julho de 2016 Published on 26-09-2016
Pamidran (sodium pamidronate)	***Information for patients*** Cartão de Alerta para o Doente – 1.ª versão aprovada em setembro de 2016 Published on 30-09-2016
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Compiled by Magda Pedro

Communications to Healthcare Professionals

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