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:

![Volume labels](image)

– **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*
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 is a tetracycline that is indicated in the treatment of complicated intra-abdominal 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. This decrease was more pronounced in the patients who received higher doses of tigecycline.

Based on these and other cases in the literature, 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

References:
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 guidelines1-10.

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

References:
8 Circular Informativa n.º 006/CD/550.20.001, de 29/01/2016
9 Circular Informativa n.º 151/CD/550.20.001, de 20/10/2016

What do they stand for?

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee (EMA)</td>
</tr>
<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of the Product’s Characteristics</td>
</tr>
</tbody>
</table>
### Educational Materials published on the Infarmed website

#### Medicinal product (DCI) | Click on the links (in Portuguese)
---|---
**Darzalex** (daratumumab) &lsquo;Information for healthcare professionals'  
Brochura para profissionais de Bancos de Sangue (BBD)  
1.ª versão aprovada em setembro de 2016  
Brochura para profissionais de saúde (HCP)  
1.ª versão aprovada em setembro de 2016  
'Information for patients'  
Cartão do doente – 1.ª versão aprovada em setembro de 2016

**Imlygic** (talimogene laherparepvec) &lsquo;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) &lsquo;Information for patients'  
Cartão de Alerta para o Doente – 1.ª versão aprovada em setembro de 2016  
Published on 30-09-2016

**Stelara** (ustecinumab) &lsquo;Information for healthcare professionals'  
Informação de segurança importante para o profissional de saúde  
6.ª versão aprovada em março de 2016  
Instruções de utilização para o profissional de saúde  
3.ª versão aprovada em março de 2016  
Instruções de utilização para o profissional de saúde (brochura)  
3.ª versão aprovada em março de 2016  
'Information for patients'  
Informação de segurança para o doente – 6.ª versão aprovada em março de 2016  
Instruções de utilização para o doente – 3.ª versão aprovada em março de 2016  
Instruções de utilização para o doente (brochura)  
3.ª versão aprovada em março de 2016  
Published on 28-09-2016

**Uptravi** (selexipag) &lsquo;Information for healthcare professionals'  
Carta de apresentação para o profissional de saúde  
1.ª versão aprovada em agosto de 2016  
Guia de titulação do profissional de saúde – 1.ª versão aprovada em agosto de 2016  
Published on 11-10-2016

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### Communications to Healthcare Professionals

#### Medicinal product (DCI) | Click on topic for details (in Portuguese)
---|---
**ellaOne** (ulipristal acetate)  
Postmarketing surveillance of this emergency contraception method by means of a pregnancy registry  
Published on 10-10-2016

**Reminyl** (galantamine)  
Serious cutaneous adverse reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis)  
Published on 26-09-2016

Compiled by Magda Pedro

Compiled by Ana Sofia Martins