13 October 2016
EMA/PRAC/634818/2016 Rev[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 26-29 September 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 26-29 September 2016 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (10-13 October 2016) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] The recommendation for levetiracetam was updated on 21 November 2017 (see highlighted paragraphs on pages 4-5).
[2] The relevant EPITT reference number should be used in any communication related to a signal.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[3]

1.1. Levetiracetam (oral solution) – Medication errors associated with accidental overdose

Authorisation procedure	Centralised and non-centralised
EPITT No	10519
PRAC rapporteur(s)	Veerle Verlinden (BE)
Date of adoption	29 September 2016

Recommendation *[see also section 3]*

Having considered the available evidence, including the additional information submitted by the MAH on the risk of medication errors associated with accidental overdoses of Levetiracetam oral solution, the PRAC has agreed that all MAHs of levetiracetam oral solution formulation should submit a variation within 2 months, to amend the Package Leaflet (PL) as described below (new text underlined).

Package leaflet

3 – How to take Keppra

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day. Take the oral solution following your doctor's instructions.

Monotherapy

Dose in adults and adolescents from ~~(~~16 years of age~~)~~:
Measure the appropriate dosage using the 10 ml syringe included in the package for patients 4 years and above.
General dose: ~~between 10 ml (1000 mg) and 30 ml (3,000 mg) each day, divided in 2 intakes per day.~~
Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).
When you will first start taking Keppra, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest general dose.

Add-on therapy

Dose in adults and adolescents (12 to 17 years) weighing 50 kg or more:

Measure the appropriate dosage using the 10 ml syringe included in the package for patients of 4 years and above.
General dose: ~~between 10 ml (1,000 mg) and 30 ml (3,000 mg) each day, divided in 2 intakes per day.~~
Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

Dose in children 6 months and older ~~weighing less than 50 Kg Dose in infants (6 to 23 months), children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg~~:
Your doctor will prescribe the most appropriate pharmaceutical form of Keppra according to the age, weight and dose.

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

For children 6 months to 4 years, measure the appropriate dosage using the 3 ml syringe included in the package.
For children above 4 years, measure the appropriate dosage using the 10 ml syringe included in the package.
General dose: Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 0.1 ml (10mg) and 0.3 ml (30mg), per kg bodyweight of the child. (see table below for dose examples).
~~Your doctor will prescribe the most appropriate pharmaceutical form of Keppra according to the age, weight and dose.~~
~~General dose: between 0.2 ml (20 mg) and 0.6 ml (60 mg) per kg bodyweight each day, divided in 2 intakes per day.~~
~~The exact quantity of oral solution formulation should be delivered using the syringe provided in the cardboard box.~~

Dose in children 6 months and older ~~weighing less than 50 kg~~:

Weight	Starting dose: 0.1 ml/kg twice daily	Maximum dose: 0.3 ml/kg twice daily
6 kg	0.6 ml twice daily	1.8 ml twice daily
8 kg	0.8 ml twice daily	2.4 ml twice daily
10 kg	1 ml twice daily	3 ml twice daily
15 kg	1.5 ml twice daily	4.5 ml twice daily
20 kg	2 ml twice daily	6 ml twice daily
25 kg	2.5 ml twice daily	7.5 ml twice daily
From 50 kg	5 ml twice daily	15 ml twice daily

Dose in infants (1 month to less than 6 months):
For infants 1 month to less than 6 months, measure the appropriate dosage using the **1 ml** syringe included in the package.
General dose: Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 0.07 ml (7mg) and 0.21 ml (21mg), per kg bodyweight of the infant. (see table below for dose examples).
~~General dose: between 0.14 ml (14 mg) and 0.42 ml (42 mg) per kg bodyweight each day, divided in 2 intakes per day. The exact quantity of oral solution formulation should be delivered using the syringe provided in the cardboard box.~~

Dose in infants (1 month to less than 6 months):

Weight	Starting dose: 0.07 ml/kg twice daily	Maximum dose: 0.21 ml/kg twice daily
4 kg	0.3 ml twice daily	0.85 ml twice daily
5 kg	0.35 ml twice daily	1.05 ml twice daily
6 kg	0.45 ml twice daily	1.25 ml twice daily
7 kg	0.5 ml twice daily	1.5 ml twice daily

Method of administration:
After measuring the correct dose with an appropriate syringe, Keppra oral solution may be diluted in a glass of water or baby's bottle.

Outer packaging and labels[4]
Colour codes should be used to differentiate each presentation by age ranges and the same colour should be used both on the outer packaging and labels of the presentation that is intended to: (i) blue for the 150ml bottle with 1ml syringe; (ii) green for the 150ml bottle with 3ml syringe; (iii) orange for the 300ml bottle with 10ml syringe.

[4] These three paragraphs on 'Outer packaging and labels' were made publicly available on 21 November 2017.

Pictograms should be added to both outer packaging and labels to facilitate the identification of the (i) bottle size, (ii) the syringe volume and (iii) the correct age group to which the presentation is intended to. The pictograms representing the age range should be in red to draw the attention of the patient/caregiver.

In order to achieve consistency in adherence with the recommended minimisation measures, MAHs with more than one presentation of oral solution should make efforts to (i) differentiate one presentation from another (following the above colour code, when applicable), (ii) clearly state the age range for whom the presentation is intended (front warning on packaging and labelling), and (iii) clearly state on the packaging/labelling which dosing device should be used with a specific presentation. MAHs marketing generic levetiracetam oral solution formulations should liaise directly with their respective competent authorities to implement the recommended changes in order to minimise the risk of accidental overdoses associated with medication error.

1.2. Metronidazole – Severe hepatic and neurologic toxicity in patients with Cockayne syndrome

Authorisation procedure	Non-centralised
EPITT No	18663
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	29 September 2016

Recommendation *[see also section 3]*

Having considered the available evidence on the association between hepatotoxicity and metronidazole exposure in patients with Cockayne syndrome, the PRAC has agreed that the MAHs of metronidazole-containing medicinal products (except for external use on the skin) should submit a variation within 2 months, to amend the product information as described below (new text underlined). Communication of the update of the product information should be agreed on a national basis, as necessary.

Summary of product characteristics

4.4. Special warnings and precautions for use

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Package leaflet

2 – What you need to know before you use metronidazole

Warnings and precautions

Cases of severe liver toxicity/acute liver failure, including cases with a fatal outcome, in patients with Cockayne syndrome have been reported with product containing metronidazole.

If you are affected by Cockayne syndrome, your doctor should also monitor your liver function frequently while you are being treated with metronidazole and afterwards.

Tell your doctor immediately and stop taking metronidazole if you develop:

- Stomach pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine, putty or mastic coloured stools or itching.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dexlansoprazole; lansoprazole	Unexpected histopathological findings from a juvenile rat toxicity study (18645)	Kirsti Villikka (FI)	Supplementary information requested (submission by 7 December 2016)	Takeda
Lenvatinib	Cholecystitis (18750)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 7 December 2016)	Eisai Europe Ltd
Nivolumab	Pemphigoid (18759)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 December 2016)	Bristol-Myers Squibb Pharma EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Acute febrile neutrophilic dermatosis (Sweet's syndrome) (18630)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	AbbVie Ltd

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Anakinra; canakinumab	Weight increased (18641)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Swedish Orphan Biovitrum AB (publ); Novartis Europharm Ltd
Fluoroquinolones (for systemic use): ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Aortic aneurysm and dissection (18651)	Valerie Strassmann (DE)	Routine pharmacovigilance	MAHs of fluoroquinolones for systemic use
Levetiracetam (oral solution)	Medication errors associated with accidental overdose (10519)	Veerle Verlinden (BE)	Single direct healthcare professional communication (DHPC) requested; monitor in PSUR	MAHs of levetiracetam oral solution
Medicinal products belonging to the same chemical/ pharmacological group as metronidazole (e.g. nitroimidazoles)	Severe hepatic and neurologic toxicity in patients with Cockayne syndrome (18663)	Martin Huber (DE)	Monitor in PSUR	MAHs of products belonging to the same chemical/ pharmacological group as metronidazole
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment (17796)	Veerle Verlinden (BE)	No action at this stage	Not applicable
Propofol	Diabetes insipidus (18622)	Kristin T. Kvande (NO)	Routine pharmacovigilance	MAHs of propofol containing products
Regorafenib	Angioedema (18656)	Sabine Straus (NL)	Routine pharmacovigilance	Bayer Pharma AG