7 January 2025[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 25-28 November 2024 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 25-28 November 2024 (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 (9-12 December 2024) 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] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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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. Azathioprine – Non-cirrhotic portal hypertension / portosinusoidal vascular disease

Authorisation procedure	Centralised and non-centralised
EPITT No	20091
PRAC Rapporteur	Karin Erneholm (DK)
Date of adoption	28 November 2024

Recommendation

Having considered the available evidence in EudraVigilance and from the literature, and the cumulative reviews submitted by the contacted marketing authorisation holders (MAHs), the PRAC has agreed that all the MAHs of medicinal products containing azathioprine should submit a variation within 2 months of the publication of the PRAC recommendation, to amend the product information as described below (new text underlined, removed text ~~strikethrough~~):

Summary of product characteristics (SmPC)

In case the SmPC already includes a similar or stricter wording regarding liver damage, the similar or stricter advice remains valid and should remain. If the SmPC contains statements indicating hepatic damage is primarily described in transplant patients, these statements should be deleted.

4.4 Special warnings and precautions for use

A warning should be amended/added as follows:

Monitoring

[…]

Azathioprine is hepatotoxic and liver function tests should be routinely monitored during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. Cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported. Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly (see section 4.8). The patient should be informed about the symptoms of liver injury and advised to contact their doctor immediately if these occur ~~instructed to discontinue azathioprine immediately if jaundice becomes apparent~~.

4.8. Undesirable effects

The following adverse reactions should be added under the SOC Hepatobiliary disorders with a frequency "Not known":

Non-cirrhotic portal hypertension, portosinusoidal vascular disease

Additionally, the text below should be amended to the section "Description of selected adverse reactions"

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

Hepatobiliary disorders

[…]

Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described ~~primarily in transplant patients~~. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. In some cases, withdrawal of azathioprine has resulted in either temporary or permanent improvement in liver histology and the symptoms.

Package leaflet

In case the package leaflet already includes a similar or stricter wording regarding liver damage, the similar or stricter advice remains valid and should remain. If the package leaflet contains statements indicating liver damage is primarily described in transplant patients, these statements should be deleted.

2. What you need to know before you take [product name]

Warning and precautions

Liver damage

Treatment with [product name] may affect the liver and your doctor will monitor your liver function regularly. Tell your doctor if you experience symptoms of liver damage (see section 4 "Possible side effects").

4. Possible side effects

If you get any of the following serious side effects, talk to your doctor or go to hospital immediately:

[…]

Not known (frequency cannot be estimated from the available data)

Severe liver damage which can be life threatening, especially in ~~transplant~~ patients who receive long-term treatment (like liver injury, non-cirrhotic portal hypertension, portosinusoidal vascular disease). Tell your doctor if you experience any of the following symptoms: yellowing of the skin and the whites of the eyes (jaundice), bruising easily, abdominal discomfort, loss of appetite, fatigue, nausea, or vomiting.

In case the adverse event is already listed in the package leaflet with another frequency, the existing frequency should be maintained.

1.2. Nitric oxide – Pulmonary oedema in patients with veno-occlusive disease

Authorisation procedure	Centralised and non-centralised
EPITT No	20086
PRAC Rapporteur	Jo Robays (BE)
Date of adoption	28 November 2024

Recommendation

Having considered the available data in EudraVigilance and the literature, including the cumulative review submitted by the MAHs, the PRAC has agreed that the MAHs of nitric oxide containing-products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4 Special warnings and precautions for use

Pulmonary veno-occlusive disease

Cases of life-threatening pulmonary oedema have been reported with nitric oxide when used in patients with pulmonary veno-occlusive disease. Therefore, the possibility of a veno-occlusive disease should be carefully evaluated if signs of pulmonary oedema occur following the administration of nitric oxide to patients with pulmonary hypertension. If confirmed, treatment is to be discontinued.

Package leaflet

2. What you need to know before you take [product name]

Warnings and precautions

Cases of fluid retention in the lungs have been reported with nitric oxide in patients with disease due to a blocked or narrow vein in the lungs. If you (as a patient) or your child (as a patient) develops shortness of breath or difficulty breathing, contact your doctor immediately.

1.3. Risperidone oral solution – Medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution

Authorisation procedure	Non-centralised
EPITT No	20085
PRAC Rapporteur	Martin Huber (DE)
Date of adoption	28 November 2024

Recommendation

Having considered the available evidence, including the additional information submitted by the MAH on the risk of medication errors associated with accidental overdoses in children and adolescents treated with risperidone oral solution, the PRAC has agreed that all MAHs of risperidone oral solution formulations should provide dosing devices with a clearly legible, written label in 0.25 ml intervals.

Smaller intervals like 0.05 ml should be marked with lines but are not expected to be labelled with written numbers.

MAHs are requested to include clear instructions along with illustrations in the patient leaflet to educate the patients and caregivers on measuring volumes correctly, particularly small volumes. Due to the variability of dosing devices across products, no figures can be recommended within this procedure. Each MAH should introduce appropriate illustrating figures matching the specific dosing device delivered with their risperidone oral solution. These requirements should be implemented within a type II variation submitted within 6 months from the publication of the PRAC recommendation. For harmonisation purposes, work-sharing variations are to be considered, where applicable.

Within the same variation requested above, MAHs of risperidone oral solution formulation should amend the package leaflet as described below, taking into account the already existing wording in nationally authorised products as the text needs to be adapted by MAHs to individual products (new text underlined, text to be removed ~~strike through~~):

Package leaflet

3. How to take [product name]

Method of administration

FOR ORAL USE

The solution comes with a <dosing device, i.e. pipette or syringe>. Use only the <dosing device> delivered with this medicine for measuring the dose prescribed by the physician. ~~This should be used to help you m~~Measure the exact ~~amount~~ dose of medicine you need. Pay attention when measuring a small dose, for example for 0.25 mg, measure 0.25 ml (a quarter millilitre); for 0.5 mg, measure 0.5 ml (half a millilitre).

Follow these steps:

…

7. Rinse the <dosing device, i.e. pipette or syringe> with some water and let it air dry.

A DHPC for pharmacists to advise the patients on the correct use of the dosing devices might be considered at the discretion of the national competent authorities.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Paradoxical hidradenitis (20126)	Karin Bolin (SE)	Supplementary information requested (submission by 5 February 2025)	AbbVie Deutschland GmbH & Co. KG
Emtricitabine, tenofovir disoproxil	Trigeminal neuralgia (20121)	Ana Sofia Diniz Martins (PT)	Supplementary information requested (submission by 5 February 2025)	Gilead Sciences Ireland UC
Regorafenib	Nephrotic syndrome (20123)	Bianca Mulder (NL)	Supplementary information requested (submission by 5 February 2025)	Bayer AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Doxycycline	Suicidality (19997)	Liana Martirosyan (NL)	Monitor in PSURs	MAHs of doxycycline-containing products with the obligation to submit PSURs
Rosuvastatin	Tubulointerstitial nephritis (20084)	Bianca Mulder (NL)	· Monitor in PSURs · Provide a cumulative review of increased creatinine levels in the next PSUR (submission by 4 February 2028)	Grünenthal