25 November 2024[1]
EMA/PRAC/499603/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 28-31 October 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 28-31 October 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 (11-14 November 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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Angiotensin II receptor blockers (ARBs): azilsartan; candesartan; eprosartan; irbesartan; losartan; olmesartan; telmisartan; valsartan (single ingredient and fixed dose combinations) – Intestinal angioedema

Authorisation procedure	Centralised and non-centralised
EPITT No	20104
PRAC Rapporteur	Martin Huber (DE)
Date of adoption	31 October 2024

Recommendation

Having considered the available evidence in EudraVigilance for Angiotensin II receptor blockers (ARBs), including the cumulative reviews submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs of olmesartan-, irbesartan-, valsartan-, losartan-, candesartan-, azilsartan-, eprosartan- and telmisartan-containing products (mono-substances and fixed-dose combinations) should submit a variation within 2 months from the publication of the PRAC recommendation to amend the product information as described below, taking into account the already existing wording in some nationally authorised products where the text needs to be adapted by MAHs to individual products (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

For olmesartan, irbesartan, valsartan, losartan and candesartan:

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including <INN>] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

For azilsartan, eprosartan and telmisartan:

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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

4.8. Undesirable effects

For olmesartan, irbesartan, valsartan, losartan, and candesartan: addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":

SOC Gastrointestinal disorders

Intestinal angioedema

For azilsartan, eprosartan and telmisartan:

Description of selected adverse reactions:

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

Package leaflet

For all ARBs (olmesartan, azilsartan, candesartan, eprosartan, irbesartan, valsartan, losartan and telmisartan):

2. What you need to know before you take X

Warnings and precautions

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking <X>. Your doctor will decide on further treatment. Do not stop taking <X> on your own.

4. Possible side effects

For olmesartan, irbesartan, valsartan, losartan and candesartan addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":

Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea

For azilsartan, eprosartan and telmisartan:

Frequency 'not known': Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhoea has been reported after the use of similar products.

1.2. Paracetamol (single ingredient and fixed dose combinations) – High anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis

Authorisation procedure	Non-centralised
EPITT No	20105
PRAC Rapporteur	Jean-Michel Dogné (BE)
Date of adoption	31 October 2024

Recommendation

Having considered all the available evidence, including data from EudraVigilance and the literature, the PRAC has agreed that the product information of all paracetamol-containing medicinal products (single-ingredient and fixed dose combinations) should be amended to provide additional clarity on the risk of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis. The PRAC considered the comments on the proposed amendment of the product information provided by the MAHs of paracetamol (single-ingredient and fixed dose combinations): Haleon; Upsa SAS; Opella Healthcare; Teva; Zentiva; Laboratoires SMB; GlaxoSmithKline; Angelini Pharma; Stada and Johnson & Johnson.

The PRAC has agreed that the MAHs of all paracetamol-containing medicinal products (single-ingredient and fixed dose combinations), including the MAHs mentioned in the above paragraph, 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, deleted text ~~strike through~~). Considering the already existing wording in some nationally authorised products, the text may need to be adapted by MAHs to individual products.

Summary of product characteristics

4.4. Special warnings and precautions for use

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported ~~Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly~~ in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin.~~as well as those using maximum daily doses of paracetamol.~~ If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring~~, including measurement of urinary 5-oxoproline,~~ is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

4.5. Interaction with other medicinal products and other forms of interaction

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

4.8. Undesirable effects

SOC: Metabolism and nutrition disorders

"High anion gap metabolic acidosis'' with frequency ''Not known'' (cannot be estimated from the available data)

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

During treatment with <product name>, tell your doctor straight away if:

[…]

If you have severe illnesses, including severe renal impairment or sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), or you suffer from malnutrition, chronic alcoholism or if you are also taking flucloxacillin (an antibiotic). A serious condition called metabolic acidosis (a blood and fluid abnormality) has been reported in patients in these situations when paracetamol is used at regular doses for a prolonged period or when paracetamol is taken together with flucloxacillin. Symptoms of metabolic acidosis may include: serious breathing difficulties with deep rapid breathing, drowsiness, feeling sick (nausea) and being sick (vomiting).

Other medicines and paracetamol

Please inform your doctor or pharmacist if you are taking:

- flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (called metabolic acidosis) that must have urgent treatment (see section 2).~~, and which may occur particularly in case of patients with severe illness, including severe renal impairment, sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), malnutrition, chronic alcoholism, or when and if the maximum daily doses of paracetamol are is used for a prolonged period.~~

4. Possible side effects

Frequency "Not known'' (frequency cannot be estimated from the available data): "A serious condition that can make blood more acidic (called metabolic acidosis), in patients with severe illness using paracetamol (see section 2)"

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Avelumab; atezolizumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; pembrolizumab; retifanlimab; tislelizumab; toripalimab; tremelimumab	Scleroderma, systemic scleroderma, morphea (20119)	David Olsen (NO)	Supplementary information requested (submission by 8 January 2025)	Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V., AstraZeneca AB, Merck Europe B.V., Roche Registration GmbH, Regeneron Ireland Designated Activity Company (DAC), GlaxoSmithKline (Ireland) Limited, Beigene Ireland Limited, Incyte Biosciences Distribution B.V., TMC Pharma (EU) Ltd
Domperidone	Hypertension in patients with a phaeochromocytoma (20106)	Jean-Michel Dogné (BE)	Assess in the next PSUR (submission by 17 February 2025)	Johnson & Johnson
Ixekizumab	Demyelinating disorders (20124)	Gabriele Maurer (DE)	Supplementary information requested (submission by 8 January 2025)	Eli Lilly and Co (Ireland) Limited
Tegafur, gimeracil, oteracil	Hyperammonaemia (20115)	Bianca Mulder (NL)	Supplementary information requested (submission by 8 January 2025)	Nordic Group B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Eptinezumab; erenumab; fremanezumab; galcanezumab	Insomnia (20077)	Terhi Lehtinen (FI)	Routine pharmacovigilance	H. Lundbeck A/S, Novartis Europharm Limited, TEVA GmbH, Eli Lilly Nederland B.V.