22 November 2021[1]
EMA/PRAC/605613/2021 Corr[2]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 25-28 October 2021 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 October 2021 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][3] 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 (8-11 November 2021) 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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] A minor editorial amendment was implemented in the labetalol product information on 9 December 2021 (see page 4).
[3] The relevant EPITT reference number should be used in any communication related to a signal.

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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.

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[4]

1.1. Ertapenem – Toxic encephalopathy in patients with renal impairment

Authorisation procedure	Centralised and non-centralised
EPITT No	19498
PRAC rapporteur(s)	Ana Sofia Diniz Martins (PT)
Date of adoption	28 October 2021

Recommendation *[see also section 3]*

Based on review of the available evidence ascertained from EudraVigilance and the literature, PRAC considers that there is a reasonable possibility of causality concerning events of encephalopathy in association with ertapenem and that recovery in patients with renal impairment maybe prolonged. The PRAC recommends that the MAH for Invanz, Merck Sharp & Dohme B.V., should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the Summary of Product Characteristics as described below (new text underlined and in **bold**). No changes to the package leaflet are considered necessary as symptoms associated with encephalopathy are already described.

Summary of product characteristics

4.4. Special warnings and precautions for use

Encephalopathy

Encephalopathy has been reported with the use of ertapenem (see section 4.8). If ertapenem-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness), discontinuation of ertapenem should be considered. Patients with renal impairment are at higher risk of ertapenem-induced encephalopathy and the resolution may be prolonged.

4.8. Undesirable effects

	Adults 18 years of age and older	*Children and adolescents (3 months to 17 years of age)*
Nervous system disorders	*Common*: Headache *Uncommon*: Dizziness, somnolence, taste perversion, seizure (see section 4.4) *Rare*: Tremor, syncope *Not known*: Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance, **encephalopathy (see section 4.4)**	*Uncommon*: Headache *Not known*: Hallucinations

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

1.2. Labetalol – nipple pain and suppressed lactation

Authorisation procedure	Non-centralised
EPITT No	19639
PRAC rapporteur(s)	Karen Pernille Harg (NO)
Date of adoption	28 October 2021

Recommendation

The PRAC has considered the available evidence in databases including EudraVigilance, the literature, and the data submitted by Aspen Pharma regarding the risk of nipple pain and suppressed lactation associated with labetalol. The data on suppressed lactation is not sufficiently strong to warrant changes in the product information at this stage, however these events should continue to be monitored as part of routine safety surveillance.

The PRAC has agreed that the MAH(s) of labetalol 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

4.6. Fertility, pregnancy and lactation

Breast-feeding

~~No side effects have been reported to date.~~[5]

- Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4.8).

4.8. Undesirable effects

Reproductive system and breast disorders

Frequency 'not known': Nipple pain, Raynaud's phenomenon of the nipple

Package leaflet

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

Pregnancy, breast-feeding and fertility

- Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4).

4. Possible side effects

Not known (cannot be estimated from the available data)

- Nipple pain
- Intermittent decrease in blood flow to your nipples, which may cause your nipples to go numb, pale, and painful (Raynaud's phenomenon)

[5] Added on 9 December 2021.

1.3. Lenvatinib – Colitis

Authorisation procedure	Centralised
EPITT No	19691
PRAC rapporteur(s)	Annika Folin (SE)
Date of adoption	28 October 2021

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of lenvatinib-containing medicinal 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

4.8. Undesirable effects

Gastrointestinal disorders

Frequency 'uncommon': Colitis

Package leaflet

4. Possible side effects

Other side effects include:

Uncommon (may affect up to 1 in 100 people)

Inflammation of the colon (colitis)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Alemtuzumab	Vitiligo (19737)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 5 January 2022)	Sanofi Belgium
COVID-19 mRNA[6] vaccine (nucleoside-modified) – Comirnaty	Myocarditis and pericarditis (19712)	Menno van der Elst (NL)	Supplementary information requested (submission by 15 November 2021)	BioNTech Manufacturing GmbH
COVID-19 mRNA[4] vaccine (nucleoside-modified) - Spikevax	Capillary leak syndrome (19743)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 26 November 2021)	Moderna Biotech Spain, S.L.
COVID-19 mRNA[4] vaccine (nucleoside-modified) - Spikevax	Myocarditis and pericarditis (19713)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 15 November 2021)	Moderna Biotech Spain, S.L.
Sacubitril, valsartan	Vasoplegia syndrome (19739)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 5 January 2022)	Novartis Europharm Limited
Tocilizumab	Encephalopathy including posterior reversible encephalopathy syndrome (PRES) (19731)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 5 January 2022)	Roche Registration GmbH

[6] Messenger ribonucleic acid

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Acquired haemophilia (19688)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	MAHs of adalimumab-containing products
COVID-19 mRNA[7] vaccine (nucleoside-modified) – Comirnaty; COVID-19 mRNA[5] vaccine (nucleoside-modified) – Spikevax; COVID-19 vaccine (Ad26.COV2-S [recombinant]) - COVID-19 Vaccine Janssen; COVID-19 vaccine (ChAdOx1-S [recombinant]) – Vaxzevria	Multisystem inflammatory syndrome (19732)	Menno van der Elst (NL)	Monitor within the monthly summary safety reports (MSSRs) and periodic safety update reports (PSURs)	BioNTech Manufacturing GmbH; Moderna Biotech Spain, S.L.; Janssen-Cilag International NV; AstraZeneca AB
Ertapenem	Toxic encephalopathy in patients with renal impairment (19498)	Ana Sofia Diniz Martins (PT)	· See section 1.1 · Submit a cumulative review within the next PSUR concerning events of peripheral neuropathy (submission by 27 June 2025)	Merck Sharp & Dohme B.V.
Ibrutinib	Sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors from a clinical trial (19726)	Nikica Mirošević Skvrce (HR)	Routine pharmacovigilance	Janssen-Cilag International NV

[7] Messenger ribonucleic acid

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Olmesartan	Autoimmune hepatitis (19258)	Martin Huber (DE)	Provide comments to the proposed updates to the product information (submission by 5 November 2021)	MAHs of olmesartan-containing products
Propylthiouracil	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19692)	Krõõt Aab (EE)	Routine pharmacovigilance	MAHs of propylthiouracil-containing products