



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 2-5 September 2019 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 2-5 September 2019 (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 (16-19 September 2019) 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 Intended publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

² A footnote was added to the ibuprofen product information on 10 October 2019 to clarify that the PRAC recommendation only applies to systemic formulations (see page 4).

³ The relevant EPITT reference number should be used in any communication related to a signal.



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 information⁴

1.1. Ibrutinib – Ischaemic stroke

Authorisation procedure	Centralised
EPITT No	19369
PRAC rapporteur(s)	Nikica Mirošević Skvrce (HR)
Date of adoption	5 September 2019

Recommendation

Having considered the available evidence and following the assessment of the data submitted by the concerned MAH, the PRAC has agreed that the product information for ibrutinib should be updated to reflect the risk of ischemic central nervous vascular conditions.

The MAH of Imbruvica (Janssen-Cilag International NV) should submit a variation within two months from the publication of the PRAC recommendation, to amend the product information as described here (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Cerebrovascular accidents

Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported with the use of ibrutinib, with and without concomitant atrial fibrillation and/or hypertension. Latency from the initiation of treatment with ibrutinib to the onset of ischemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases) emphasizing the need for regular monitoring of patients (please see section 4.4 Cardiac arrhythmia and Hypertension and section 4.8).

4.8. Undesirable effects

Tabulated list of adverse reactions

Nervous system disorders

Uncommon: cerebrovascular accident, transient ischaemic attack, ischaemic stroke

Package leaflet

2. What you need to know before you take IMBRUVICA

Warnings and precautions

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

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

4. Possible side effects

Tell a doctor straight away if you notice any of the following side effects:

Uncommon (may affect up to 1 in 100 people):

temporary episode of neurologic dysfunction caused by loss of blood flow, stroke.

1.2. Ibuprofen – Acute generalised exanthematous pustulosis (AGEP)

Authorisation procedure	Non-centralised
EPITT No	19409
PRAC rapporteur(s)	Anette Kirstine Stark (DK)
Date of adoption	5 September 2019

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of ibuprofen and acute generalised exanthematous pustulosis (AGEP), the PRAC has agreed that the MAH(s) of ibuprofen-containing medicinal products⁵ should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

1. For ibuprofen monotherapy or ibuprofen in combinations excluding combinations with pseudoephedrine

4.4. Special warnings and precautions for use

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Not known: Acute generalised exanthematous pustulosis (AGEP)

2. For ibuprofen and pseudoephedrine combinations

4.4. Special warnings and precautions for use

Severe skin reactions

⁵ Only systemic formulations

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) may occur with ibuprofen and pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of <product name> should be discontinued and appropriate measures taken if needed.

4.8. Undesirable effects¹

Skin and subcutaneous tissue disorders

Not known: Acute generalised exanthematous pustulosis (AGEP)

Package leaflet²

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

Warnings and precautions - Take special care with <product name>

Skin reactions²

Serious skin reactions have been reported in association with <product name> treatment. You should stop taking <product name> and seek medical attention immediately, if you develop any skin rash, lesions of the mucous membranes, blisters or other signs of allergy since this can be the first signs of a very serious skin reaction. See section 4.

4. Possible side effects

Frequency "Not known"

A red, scaly widespread rash with bumps under the skin and blisters mainly localized on the skin folds, trunk, and upper extremities accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis). Stop using <product name> if you develop these symptoms and seek medical attention immediately. See also section 2.

Footnotes:

1 Only if the already existing AGEP ADR in section 4.8 is listed specifically for pseudoephedrine.

2 The following text should replace any current information regarding serious skin reactions in section Warnings and precautions.

1.3. Sodium-glucose co-transporter 2 (SGLT2) inhibitors⁶ – New information on the known association between SGLT2 inhibitors and diabetic ketoacidosis in surgical patients

Authorisation procedure	Centralised
EPITT No	19355
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	5 September 2019

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the known association of sodium-glucose co-transporter 2 (SGLT2) inhibitors with diabetic ketoacidosis, the PRAC has agreed that the MAH(s) of all SGLT2i - containing medicinal products should submit a variation within 2 months, to amend the product information with a recommendation to monitor ketone bodies during surgical procedures as described below (new text underlined / text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

Diabetic ketoacidosis

[...]

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. ~~In both cases, t~~Treatment with < product name> may be restarted ~~once~~ when the ketone values are normal and the patient's condition has stabilised.

1.4. Teriflunomide – Psoriasis

Authorisation procedure	Centralised
EPITT No	19366
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	5 September 2019

Recommendation

Having considered the available evidence in EudraVigilance, the literature, clinical trials and the cumulative review provided by the MAH of Aubagio (Sanofi Genzyme) the PRAC has agreed that the MAH of Aubagio should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Skin reactions

⁶ Canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin, metformin; empagliflozin; empagliflozin, metformin; empagliflozin, linagliptin; ertugliflozin, metformin; ertugliflozin, sitagliptin; saxagliptin, dapagliflozin

[...]

New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of teriflunomide. Treatment withdrawal and initiation of an accelerated elimination procedure may be considered taking into account patient's disease and medical history.

4.8. Undesirable effects

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders

Frequency not known: Psoriasis (including pustular psoriasis)^b

b: see section 4.4

Package leaflet

4. Possible side effects

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

[...]

- Severe skin reactions
- Psoriasis

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Abiraterone	Interaction with sulphonylureas leading to hypoglycaemia (19445)	Eva A. Segovia (ES)	Supplementary information requested (submission by 6 November 2019)	Janssen-Cilag International NV
Adalimumab	Pericarditis (19457)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 6 November 2019)	AbbVie Deutschland GmbH & Co. KG
Anastrozole	Hallucinations (19449)	Zane Neikena (LV)	Supplementary information requested (submission by 6 November 2019)	AstraZeneca
Golimumab	Inflammatory myopathy (19460)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 6 November 2019)	Janssen Biologics B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ibrutinib	Neutrophilic dermatoses (19444)	Nikica Mirošević Skvrce (HR)	Assess in the next PSUR (submission by 21 January 2020)	Janssen-Cilag International NV
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Tuberculosis (19464)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 6 November 2019)	Roche Registration GmbH, Merck Europe B.V., Regeneron Ireland U.C., AstraZeneca AB, Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V.
Perampanel	Hepatotoxicity (19383)	Ghania Chamouni (FR)	Assess in the next PSUR (submission by 30 September 2019)	Eisai GmbH
Prasugrel	Severe cutaneous adverse reactions (SCARs) (19463)	Anette Kirstine Starck (DK)	Supplementary information requested (submission by 6 November 2019)	Daiichi Sankyo Europe GmbH
Sacubitril, valsartan	Ventricular arrhythmia (19448)	Hans Christian Siersted (DK)	Assess in the next PSUR (submission by 9 October 2019)	Novartis Europharm Limited
Sitagliptin and other dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin, linagliptin, saxagliptin, vildagliptin	Rhabdomyolysis (19466)	Menno van der Elst (NL)	Supplementary information requested (submission by 6 November 2019)	Merck Sharp & Dohme B.V., Takeda Pharma A/S, Boehringer Ingelheim, AstraZeneca AB, Novartis Europharm Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Durvalumab	Myasthenia gravis (19451)	David Bence Olsen (NO)	Provide comments on the proposed updates to the product information (submission by 13 September 2019); assess in the next PSUR (submission by 8 January 2020)	AstraZeneca AB
Omalizumab	Acquired haemophilia (19385)	Annika Folin (SE)	Routine pharmacovigilance	Novartis Europharm Limited
Pembrolizumab	Optic neuritis (19381)	Menno van der Elst (NL)	Routine pharmacovigilance	Merck Sharp & Dohme B.V.
Ticagrelor	Severe cutaneous adverse reactions (SCARs) (19375)	Menno van der Elst (NL)	Monitor in PSUR; update PSUR	AstraZeneca AB
Tocilizumab	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19360)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Roche Registration GmbH