



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 6-9 February 2023 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 6-9 February 2023 (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 (20-23 February 2023) 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.



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 information³

1.1. Bosutinib – Interstitial lung disease

Authorisation procedure	Centralised
EPITT No	19843
PRAC Rapporteur	Martin Huber (DE)
Date of adoption	9 February 2023

Recommendation

Having considered the available evidence from clinical studies, post-marketing cases, literature reports and the already known association of interstitial lung disease (ILD) with other drugs within the tyrosine kinase inhibitors (TKIs) class (dasatinib, imatinib, and nilotinib), the PRAC has agreed that a causal relationship between bosutinib use and occurrence of ILD is considered plausible. The MAH of Bosulif (Pfizer Europe MA EEIG) should submit a variation within two months from the publication of the PRAC recommendation, to amend the product's information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Frequency 'not known': Interstitial lung disease

Package leaflet

4. Possible side effects

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

Interstitial lung disease (disorders causing scarring in the lungs): signs include cough, difficulty breathing, painful breathing.

³ 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. Colistimethate sodium for intravenous use – Pseudo-Bartter syndrome

Authorisation procedure	Non-centralised
EPITT No	19845
PRAC Rapporteur	Adam Przybylkowski (PL)
Date of adoption	9 February 2023

Recommendation [see also section 2 for colistimethate sodium dry inhalation powder]

Having considered the evidence from case reports in the literature and the responses from the marketing authorisation holders (MAHs), the PRAC has agreed that the MAHs of colistimethate sodium for intravenous use 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

Few cases of pseudo-Bartter syndrome have been reported in children and adults with the intravenous use of colistimethate sodium. Monitoring of serum electrolytes should be started in suspected cases and appropriate management should be implemented, however, normalisation of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium.

4.8. Undesirable effects

<for SmPCs with a tabulated summary of adverse reactions:>

Metabolism and nutrition disorders: frequency “not known” - Pseudo-Bartter syndrome <as a footnote> See section 4.4.

<for SmPCs without a tabulated summary of adverse reactions:>

Pseudo-Bartter syndrome has been reported after intravenous administration of colistimethate sodium with unknown frequency (see section 4.4).

Package leaflet

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

Warning and Precautions

If you experience muscle spasm, fatigue or increased urine output at any time, tell your doctor immediately as these events may be related to a condition known as pseudo-Bartter syndrome.

4. Possible side effects

You may experience, after intravenous administration, the following symptoms that may be related to a condition known as pseudo-Bartter syndrome (see section 2):

- muscle spasm
- increase in urine output
- fatigue

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Colistimethate sodium (dry inhalation powder)	Pseudo-Bartter syndrome (19845)	Adam Przybyłkowski (PL)	Assess in the next PSUR (submission by 13 May 2023)	Teva B.V.
Etanercept	Menstrual disorder (19812)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 3 May 2023)	Pfizer Europe MA EEIG
Ipilimumab; nivolumab; pembrolizumab	Capillary leak syndrome (Opdivo, Yervoy, Keytruda) and cytokine release syndrome (Opdivo) (19880)	Menno van der Elst (NL)	Supplementary information requested (submission by 5 April 2023)	Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab; infliximab	Menstrual disorder (19812)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Abbvie, Janssen Biologics B.V.
Nivolumab	Morphoea (19839)	Martin Huber (DE)	Monitor in PSURs	Bristol-Myers Squibb Pharma EEIG
Tofacitinib	Acnes (19885)	Liana Gross-Martirosyan (NL)	Provide comments on the proposed product information update (submission by 10 March 2023)	Pfizer Europe MA EEIG