



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 7-10 February 2022 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 7-10 February 2022 (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 (21-24 February 2022) 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. Enzalutamide – Erythema multiforme

Authorisation procedure	Centrally authorised
EPITT No	19734
PRAC Rapporteur	Eva Segovia (ES)
Date of adoption	10 February 2022

Recommendation

Having considered the available evidence in EudraVigilance, the PRAC has agreed that there is at least a reasonable causal relationship between enzalutamide and erythema multiforme, and therefore concluded that the product information should be updated accordingly.

The MAH of enzalutamide-containing medicinal products (Astellas Pharma Europe B.V.) 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 / text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.8. Undesirable effects

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders:

Frequency “Not known”: Erythema multiforme

Package Leaflet

2. What you need to know before you take Xtandi

~~Severe~~serious skin rash or skin peeling, blistering and/or mouth sores have been reported in association with Xtandi treatment. Seek medical attention immediately if you notice any of these symptoms.

4. Possible side effects

Frequency “Not known”: a skin reaction that causes red spots or patches on the skin that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)

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. Obinutuzumab – Non-overt disseminated intravascular coagulation

Authorisation procedure	Centralised
EPITT No	19711
PRAC Rapporteur	Annika Folin (SE)
Date of adoption	10 February 2022

Recommendation

Having considered the available evidence from the literature and spontaneous reports, and the responses from the MAH, the PRAC has agreed that the MAH for Gazyvaro (Roche Registration GmbH) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

DIC including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyvaro. The majority of cases involved non-overt DIC, with subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters occurring within 1-2 days after the first infusion with spontaneous resolution usually occurring within one to two weeks, not requiring drug discontinuation or specific intervention. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC were identified. Patients suspected to have non-overt DIC should be monitored closely with coagulation parameters including platelets and clinical observation for signs or symptoms of overt DIC. Gazyvaro should be discontinued at first onset of suspected overt DIC and appropriate treatment initiated.

4.8. Undesirable effects

Blood and lymphatic system disorders: Frequency 'uncommon': disseminated intravascular coagulation ##

[Footnote:] ##Disseminated intravascular coagulation (DIC) including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyvaro (see section 4.4).

Package leaflet

4. Possible side effects

Uncommon (may affect up to 1 in 100 people)

Abnormal coagulation, including a serious illness where clots form all over the body (disseminated intravascular coagulation)

The PRAC also noted that Table 7 in section 4.8 of the SmPC was not in line with the Guideline on Summary of Product Characteristics whereby all adverse reactions should be included regardless of their frequency. Therefore, in a separate variation to be submitted no later than 3 months from the publication of this PRAC recommendation, section 4.8 should be revised in accordance with the SmPC Guideline and other applicable guidance as relevant (e.g. Appendix 3 to the Guideline on the clinical evaluation of anticancer medicinal products). The package leaflet should be updated accordingly.

1.3. Sorafenib – Tumour lysis syndrome

Authorisation procedure	Centralised
EPITT No	19733
PRAC Rapporteur	Annika Folin (SE)
Date of adoption	10 February 2022

Recommendation

Having considered the available evidence, including the data submitted by the MAH (Bayer AG), the PRAC has agreed that the MAH 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 and in bold):

Summary of product characteristics

4.4. Special warnings and precautions for use

Tumour lysis syndrome (TLS)

Cases of TLS, some fatal, have been reported in postmarketing surveillance in patients treated with sorafenib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

4.8. Undesirable effects

The following adverse reaction should be added under the SOC Metabolism and nutrition disorders:

Frequency 'not known': **tumour lysis syndrome**

Package leaflet

2. What do you need to know before you take Nexavar

Take special care with Nexavar

- If you experience the following symptoms, contact your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness. These may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the break-down products of dying cancer cells (Tumour lysis syndrome (TLS)) and can lead to changes in kidney function and acute renal failure (see also section 4: Possible side effects).

4. Possible side effects

Not known: frequency cannot be estimated from the available data

- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness (Tumour lysis syndrome (TLS)) (see section 2).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 mRNA vaccine (nucleoside-modified) – Spikevax	Amenorrhoea (19781)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 April 2022)	Moderna Biotech Spain, S.L.
COVID-19 mRNA vaccine (nucleoside-modified) – Spikevax	Heavy menstrual bleeding (19780)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 April 2022)	Moderna Biotech Spain, S.L.
Tocilizumab	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19360)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 April 2022)	Roche Registration GmbH
Tozinameran (COVID-19 mRNA vaccine [nucleoside modified]) – Comirnaty	Amenorrhoea (19784)	David Olsen (NO)	Supplementary information requested (submission by 7 April 2022)	BioNTech Manufacturing GmbH
Tozinameran (COVID-19 mRNA vaccine [nucleoside modified]) – Comirnaty	Heavy menstrual bleeding (19783)	David Olsen (NO)	Supplementary information requested (submission by 7 April 2022)	BioNTech Manufacturing GmbH

3. Other recommendations

Not applicable