EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 July 2023[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 3-6 July 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 3-6 July 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 (17-20 July 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.

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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. Olaparib – Hepatocellular damage and hepatitis

Authorisation procedure	Centralised
EPITT No	19846
PRAC Rapporteur	Amelia Cupelli (IT)
Date of adoption	6 July 2023

Recommendation

Having considered the available evidence in EudraVigilance, the literature, nonclinical and clinical studies, the PRAC has agreed that the Marketing Authorisation Holder (MAH) AstraZeneca for Lynparza (olaparib) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text to be added **bold underlined**):

Summary of product characteristics

4.4. Special warnings and precautions for use

Hepatotoxicity

Cases of hepatotoxicity have been reported in patients treated with olaparib (see section 4.8). If clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected drug-induced liver injury (DILI), treatment should be interrupted. In case of severe DILI treatment discontinuation should be considered as clinically appropriate.

4.8. Undesirable effects

Table 1 Tabulated list of adverse reactions

MedDRA System Organ Class	Frequency of All CTCAE grades
Hepatobiliary disorders	**Not known** **Drug-induced liver injury*** **Common** **Transaminases increased[a]**

*** As observed in the post-marketing setting.**

[a] Transaminases increased includes PTs of alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and hypertransaminasaemia.

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

Package leaflet

2. What you need to know before you take Lynparza

Warnings and precautions

Talk to your doctor, pharmacist or nurse before or during treatment with Lynparza:

- **if you notice yellowing of your skin or the whites of your eyes, abnormally dark urine (brown coloured), pain on the right side of your stomach area (abdomen), tiredness, feeling less hungry than usual or unexplained nausea and vomiting contact your doctor immediately as this may indicate problems with your liver**

4. Possible side effects

Other side effects include

not known (cannot be estimated from available data)

- **Signs of liver problems, such as yellowing of your skin or the whites of your eyes (jaundice), nausea or vomiting, pain on the right side of your stomach area (abdomen), dark urine (brown coloured), feeling less hungry than usual, tiredness**

Common (may affect up to 1 in 10 people)

- […….] **abnormal liver function tests**

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel	Progressive multifocal leukoencephalopathy (PML) (19940)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 27 September 2023)	Kite Pharma EU B.V.
Dabrafenib; trametinib	Peripheral neuropathy (19947)	David Olsen (NO)	Supplementary information requested (submission by 27 September 2023)	Novartis Europharm Limited
Encorafenib; binimetinib	Tumour lysis syndrome (19941)	Inês Ribeiro-Vaz (PT)	Assess in the next PSUR (submission by 4 September 2023)	Pierre Fabre Medicament
Ixazomib	Angioedema and anaphylactic reaction (19950)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 28 July 2023)	Takeda Pharma A/S
Liraglutide	Drug-induced liver injury (19949)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 30 March 2024)	Novo Nordisk A/S
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; liraglutide; insulin degludec, liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Suicidal ideation and self-injurious ideation (19946)	Menno van der Elst (NL)	Supplementary information requested (submission by 30 August 2023)	Novo Nordisk A/S, AstraZeneca AB, Eli Lilly Nederland B.V., Sanofi Winthrop Industrie

3. Other recommendations

Not applicable