30 June 2025[1]
EMA/PRAC/179172/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 2-5 June 2025 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 June 2025 (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 (16-19 June 2025) 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. Ciltabtagene autoleucel – Immune-mediated enterocolitis / immune effector cell-associated enteritis with CAR T-cell products

Authorisation procedure	Centralised
EPITT No	20133
PRAC Rapporteur	Jo Robays (BE)
Date of adoption	5 June 2025

Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance, including the cumulative review submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAH of Carvykti (Janssen-Cilag International NV) should submit a variation within 2 months from the publication of the PRAC recommendation to amend product information as described below (new text underlined).

Summary of product characteristics

4.4 Special warnings and precautions for use

Immune-mediated enterocolitis

Patients may develop immune-mediated enterocolitis, which may emerge several months after Carvykti infusion. Some cases may be refractory to treatment with corticosteroids, and other treatment options may be relevant to consider. There were events of gastrointestinal perforation, including fatal outcomes.

4.8 Undesirable effects

Table 4: Adverse reactions in patients with multiple myeloma treated with CARVYKTI

Table of adverse reactions under the SOC Gastrointestinal disorders

Immune-mediated enterocolitis with frequency 'Common'

Package leaflet

4. Possible side effects

Other side effects

Common (may affect up to 1 in 10 people)

- Gastroenteritis, immune-mediated enterocolitis (inflamed stomach and gut)

[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. Brodalumab – Pyoderma gangrenosum

Authorisation procedure	Centralised
EPITT No	20162
PRAC Rapporteur	Monica Martinez Redondo (ES)
Date of adoption	5 June 2025

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of KYNTHEUM, LEO PHARMA A/S, 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

System Organ Class: Skin and subcutaneous tissue disorders

Adverse reaction: Pyoderma gangrenosum Frequency: Not known

Package leaflet

4. Possible side effects

Other side effects

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

- Painful swelling and skin ulceration (pyoderma gangrenosum)

The heading of the tabulated list of ADRs in KUNTHEUM SmPC refers to adverse reactions from clinical trials and post-marketing experience; in order to facilitate the current and future updates with ADRs observed from post-marketing data, the existing footnote "**from post-marketing experience*" linked to the anaphylactic reaction should be deleted from table 1.

1.3. Enzalutamide; digoxin – Laboratory test interference leading to falsely elevated digoxin plasma levels with enzalutamide

Authorisation procedure	Centralised and non-centralised
EPITT No	20134
PRAC Rapporteur	Maria del Pilar Rayon (ES)
Date of adoption	5 June 2025

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, including the cumulative review submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the laboratory interference leading to falsely elevated digoxin levels by enzalutamide should be reflected in product information of both enzalutamide and digoxin.

The PRAC has noted that the digoxin product information does not contain information on the inhibition of the efflux transporter P-gp by enzalutamide, potentially leading to increased digoxin plasma levels. The MAHs for digoxin-containing medicinal products should consider to address this topic through an appropriate regulatory procedure.

The MAHs of enzalutamide and digoxin 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):

Enzalutamide

Summary of product characteristics

4.5 Interaction with other medicinal products and other forms of interaction

P-gp substrates

In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. A mild inhibitory effect of enzalutamide, at steady-state, on P-gp was observed in a study in patients with prostate cancer that received a single oral dose of the probe P-gp substrate digoxin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The plasma levels of digoxin were measured using a validated liquid chromatography-tandem mass spectrometry assay. The AUC and Cmax of digoxin increased by 33% and 17%, respectively. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

Laboratory Test Interference

Falsely elevated digoxin plasma level results with the chemiluminescent microparticle immunoassay (CMIA) have been identified in patients treated with enzalutamide, independently of being treated with digoxin. Therefore, results of digoxin plasma levels obtained by CMIA should be interpreted with caution and confirmed by another type of assay before taking any action with digoxin doses.

Digoxin

Summary of product characteristics

4.4 Special warnings and precautions for use

Laboratory Test Interference

Falsely elevated serum levels of digoxin may occur when samples from patients receiving enzalutamide are analysed using the chemiluminescent microparticle immunoassay (CMIA), independently of being treated with digoxin. In case of doubtful results, it is recommended to confirm digoxin serum levels with an alternative assay without known interference, in order to avoid any unnecessary discontinuation or decrease in the dose of digoxin (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Determination of serum digoxin concentrations with the chemiluminescent microparticle immunoassay (CMIA) while using enzalutamide may cause falsely elevated serum digoxin levels. Results should be confirmed by another type of assay (see section 4.4).

Package leaflet

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

Other medicines and <product name>

Tell your doctor if you take a medicine containing enzalutamide (for the treatment of prostate cancer). It may interfere with your digoxin tests.

1.4. Vortioxetine – Hallucinations, not related to serotoninergic syndrome

Authorisation procedure	Centralised
EPITT No	20152
PRAC Rapporteur	Jo Robays (BE)
Date of adoption	5 June 2025

Recommendation

Having considered the available evidence from case reports including EudraVigilance, literature and the cumulative review submitted by the Marketing Authorisation Holder (MAH) of BRINTELLIX (H. Lundbeck A/S), the PRAC has agreed that MAHs for vortioxetine 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

4.8 Undesirable effects

SOC Psychiatric disorders

Hallucinations, frequency "Uncommon"

Package leaflet

4. Possible side effects

Uncommon: may affect up to 1 in 100 people

Hallucinations (seeing, hearing or feeling things that are not there)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Epcoritamab	Hypogammaglobulinaemia (20174)	Monica Martinez Redondo (ES)	Supplementary information requested (submission by 27 August 2025)	AbbVie Deutschland GmbH & Co. KG
Varicella vaccine (live)	New aspect of the known risk of encephalitis (20180)	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 18 June 2025)	GlaxoSmithKline Biologicals S.A., Merck Sharp & Dohme B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel; brexucabtagene autoleucel; ciltabtagene autoleucel; idecabtagene vicleucel; lisocabtagene maraleucel; tisagenlecleucel	Immune-mediated enterocolitis / immune effector cell-associated enteritis with CAR T-cell products (20133)	Jo Robays (BE)	· Ciltabtagene autoleucel: see section 1.1	Janssen-Cilag International NV
			· All other substances: routine pharmacovigilance	Bristol-Myers Squibb Pharma EEIG, Novartis Europharm Limited, Kite Pharma EU B.V.
Omalizumab	Hearing losses (20128)	Mari Thörn (SE)	Monitor in PSUR	Novartis Europharm Limited, Celltrion Healthcare Hungary Kft.