29 September 2025[1]
EMA/PRAC/271798/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 1-4 September 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 1-4 September 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 (15-18 September 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. Binimetinib; cobimetinib; dabrafenib; encorafenib; trametinib; vemurafenib – Tattoo associated skin reaction

Authorisation procedure	CAP
EPITT No	20160
PRAC Rapporteur	Mari Thörn (SE)
Date of adoption	4 September 2025

Recommendation *[for binimetinib, cobimetinib, encorafenib and vemurafenib, see also section 3]*

Dabrafenib and trametinib

Having considered the available evidence in EudraVigilance and the literature, including the cumulative review submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAH of MEKINIST, SPEXOTRAS (Novartis Europharm Limited) and TAFINLAR, FINLEE (Novartis Europharm Limited) should submit a variation within 2 months from the publication of the PRAC recommendation.

If more evidence becomes available in the future, the MAH of trametinib and dabrafenib should consider whether further updates of the product information regarding tattoo associated skin reactions are necessary when the respective products are used in monotherapy or the reactions are also relevant for the paediatric population.

The product information should be amended as described below (new text underlined).

Tafinlar

Summary of product characteristics

4.8 Undesirable effects

Table 4 Adverse reactions with dabrafenib in combination with trametinib

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known":

Tattoo-associated skin reactions

Package leaflet

4 Possible side effects

Possible side effects when Tafinlar and trametinib are taken together

[…]

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

- Skin reactions localised in tattoos

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

Finlee

Summary of product characteristics

4.8 Undesirable effects

Summary of the safety profile

[…]

The safety profile in paediatric patients was largely consistent with the safety profile previously established in adult patients. The following additional adverse reactions have so far only been reported in adult patients treated with dabrafenib capsules and trametinib tablets: […], drug reaction with eosinophilia and systemic symptoms ~~(frequency not known)~~, tattoo-associated skin reactions (frequency not known).

Package leaflet

4 Possible side effects

In addition to the side effects described above, the following side effects have so far only been reported in adult patients, but may also occur in children:

- Skin reactions localised in tattoos

Mekinist

Summary of product characteristics

4.8 Undesirable effects

Table 5 Adverse reactions with trametinib in combination with dabrafenib

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known":

Tattoo-associated skin reactions

Package leaflet

4 Possible side effects

Side effects when Mekinist and dabrafenib are taken together

[…]

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

- Skin reactions localised in tattoos

Spexotras

Summary of product characteristics

4.8 Undesirable effects

Summary of the safety profile

[…]

The safety profile in paediatric patients was largely consistent with the safety profile previously established in adult patients. The following additional adverse reactions have so far only been reported in adult patients treated with trametinib tablets and dabrafenib capsules: […], drug reaction with eosinophilia and systemic symptoms ~~(frequency not known)~~, tattoo-associated skin reactions (frequency not known).

Package leaflet

4 Possible side effects

In addition to the side effects described above, the following side effects have so far only been reported in adult patients, but may also occur in children:

- Skin reactions localised in tattoos

1.2. Diazoxide – Necrotising enterocolitis neonatal

Authorisation procedure	Non-centralised
EPITT No	20163
PRAC Rapporteur	Amelia Cupelli (IT)
Date of adoption	4 September 2025

Recommendation

Having considered the available evidence in EudraVigilance and the literature, including the cumulative review submitted by the Marketing Authorisation Holder/s (MAH/s), the PRAC has agreed that the MAH/s of diazoxide (RPH Pharmaceuticals AB, Merck Sharp & Dohme 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). Taking into account the already existing wording in some nationally authorised products the text may need to be adapted by MAH/s to individual products.

Summary of product characteristics

4.4 Warning and precautions for use

Necrotising enterocolitis neonatal

Cases of necrotising enterocolitis (NEC), including fatal, have been reported in neonates treated with diazoxide (see section 4.8). Patients should be monitored for symptoms such as vomiting, abdominal distension, bloody stools and lethargy, especially those with increased risk factors (such as pre-term neonates). Treatment with diazoxide should be discontinued if NEC is suspected and appropriate clinical management should be initiated.

4.8 Undesirable effects

Under SOC Gastrointestinal disorders with frequency "Not known"

Necrotising enterocolitis neonatal

Package leaflet

2. What you need to know before you take [product name]

[…]

Tell your doctor immediately, if any of the following happens to your child taking <product name>:

abdominal bloating, pain, swelling or discomfort, bloody stools, feeding intolerance (vomiting, poor feeding), lethargy as these may be signs of severe inflammation of the bowel (a condition called necrotising enterocolitis neonatal).

[…]

4. Possible side effects

Under frequency "Not known"

Intestinal inflammation with bloody stools and tissue death in newborn babies (necrotising enterocolitis neonatal).

1.3. Dinutuximab beta – Atypical haemolytic uraemic syndrome

Authorisation procedure	Centralised
EPITT No	20169
PRAC Rapporteur	Gabriele Maurer (DE)
Date of adoption	4 September 2025

Recommendation

Having considered the available evidence in EudraVigilance and the literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Qarziba (RECORDATI NETHERLANDS 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, deleted text ~~strike through~~):

Summary of product characteristics

4.4 Special warnings and precautions for use

[…]

Laboratory abnormalities

Regular~~tory~~ monitoring of liver function and electrolytes is recommended.

[…]

Atypical haemolytic uraemic syndrome

Atypical haemolytic uraemic syndrome (aHUS) has been reported in patients who received dinutuximab beta, in some cases with fatal outcome. Signs and symptoms of aHUS should be monitored for. If aHUS is diagnosed, prompt treatment is required and dinutuximab beta should be permanently discontinued.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and post-marketing are listed by system organ class and by frequency and summarised in the table below. These adverse reactions are presented by MedDRA system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), ~~and~~ uncommon (≥ 1/1,000 to < 1/100) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. ~~The type of adverse reactions seen in the post-marketing setting is consistent with the reactions seen in clinical trials.~~

[…]

Under the SOC Blood and lymphatic system disorders with a frequency 'not known':

Atypical haemolytic uraemic syndrome

Package leaflet

2 What you need to know before you use Qarziba

Warnings and precautions

[…] You might notice the following when you first receive Qarziba and during the course of treatment:
[…]

- **spinal cord and brain problems (central nervous system, CNS)**
  […]
- **symptoms of kidney failure**
  Tell your doctor or nurse if you notice an altered frequency or absence of urination.

[…]

4 Possible side effects

Addition of frequency not known:

[…]

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

- extreme tiredness and shortness of breath (which may be due to a low number of red blood cells), bleeding and bruising (which may be due to a low number of blood platelets) and kidney disease where you pass little or no urine (atypical haemolytic uraemic syndrome)

1.4. Osimertinib – Hepatitis B reactivation

Authorisation procedure	Centralised
EPITT No	20172
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	4 September 2025

Recommendation

Having considered the available evidence in EudraVigilance, the literature and the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Tagrisso (AstraZeneca AB) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described (new text underlined):

Summary of product characteristics

4.4 Special warnings and precautions for use

Hepatitis B Virus (HBV) reactivation

Hepatitis B virus reactivation can occur in patients treated with TAGRISSO, and in some cases, may result in fulminant hepatitis, hepatic failure, and death. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving TAGRISSO. In patients who develop reactivation of HBV while on TAGRISSO, treatment with TAGRISSO should be withheld and they should be managed according to local institutional guidelines.

4.8 Undesirable effects

Table 2. Under SOC Infections and infestations with frequency Not known

Hepatitis B reactivation[t]

Table footnote t Reported during post-marketing use.

(The table footnotes sequence may have to be modified depending on the location of the SOC Infections and infestations in Table 2)

Package leaflet

2. What you need to know before you take TAGRISSO

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking TAGRISSO if:

[….]

- You have ever had or might now have a hepatitis B infection. This is because TAGRISSO could cause hepatitis B virus to become active again. Tell your doctor or nurse if you get worsening tiredness or yellowing of your skin or white part of your eyes.

4 Possible side effects

Other side effects

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

Hepatitis B reactivation

1.5. Somatrogon – Lipoatrophy

Authorisation procedure	Centralised
EPITT No	20173
PRAC Rapporteur	Liana Martirosyan (NL)
Date of adoption	4 September 2025

Recommendation

Having considered the available evidence in EudraVigilance, literature and the responses of the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Ngenla, Pfizer Europe MA EEIG, 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 deleted ~~strike through~~):

Summary of product characteristics

4.2 Posology and method of administration

The site of injection should be rotated at each administration to prevent lipoatrophy (see section 4.8).

…

If more than one injection is required to deliver a complete dose, each injection should be administered at a different injection site to prevent lipoatrophy.

4.8 Undesirable effects

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known"

Lipoatrophy*

* See section 4.2

Package leaflet

3 How to use Ngenla

Fatty tissue below the skin can shrink at the site of injection (see section 4). To avoid this, use a different injection site each time.

4 Possible side effects

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

Localised loss of fat below the skin (lipoatrophy).

Instructions for use

Important information about your Ngenla pen

Each turn (click) of the dose knob increases the dose by 0.2 mg of medicine. You can give from 0.2 mg to 12 mg in a single injection. If your dose is more than 12 mg, you will need to give more than 1 injection. Each injection should be given at a different injection site.

Preparing for your injection

Step 2 Choose and clean your injection site

Choose the best place to inject, as recommended by your doctor, nurse or pharmacist. Choose a different injection site for each injection.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amlodipine	Subacute cutaneous lupus erythematosus (20203)	Karin Erneholm (DK)	Assess in the next PSUR (submission by 5 June 2027)	MAHs of amlodipine as mono-substance
Cefazolin; cefazolin, lidocaine hydrochloride	Kounis syndrome (20204)	Sonja Radowan (AT)	Supplementary information requested (submission by 3 November 2025)	Astro-Pharma GmbH
Erdafitinib	Growth accelerated (20194)	Bianca Mulder (NL)	Supplementary information requested (submission by 3 November 2025)	Janssen-Cilag International N.V.
Galantamine	Nightmares (20196)	Karin Bolin (SE)	Supplementary information requested (submission by 3 November 2025)	Janssen-Cilag International N.V.
Mepolizumab	Alopecia (20197)	Gabriele Maurer (DE)	Assess in the next PSUR (submission by 2 December 2025)	GlaxoSmithKline Trading Services Limited
Pegylated liposomal doxorubicin	Renal-limited thrombotic microangiopathy (20193)	Eva Jirsová (CZ)	Supplementary information requested (submission by 3 November 2025)	Baxter Holding B.V., Accord Healthcare S.L.U.
Pemetrexed	Lupus erythematosus (20185)	Tiphaine Vaillant (FR)	Supplementary information requested (submission by 3 November 2025)	Eli Lilly Nederland B.V.
Risankizumab	Pemphigoid (20192)	Liana Martirosyan (NL)	Supplementary information requested (submission by 3 November 2025)	AbbVie Deutschland GmbH & Co. KG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Binimetinib; cobimetinib; dabrafenib; encorafenib; trametinib; vemurafenib	Tattoo associated skin reaction (20160)	Mari Thörn (SE)	· For dabrafenib and trametinib: see section 1.1	Novartis Europharm Limited
			· For binimetinib, cobimetinib, encorafenib and vemurafenib: monitor in PSUR	Pierre Fabre Medicament, Roche Registration GmbH
Dabigatran	Splenic rupture (20164)	Marie Louise Schougaard Christiansen (DK)	Routine pharmacovigilance	Boehringer Ingelheim International GmbH
Folic acid	Increased risk of cancer with high-dose folic acid (≥1mg)	Marie Louise Schougaard Christiansen (DK)	Monitor in PSUR	MAHs of folic acid containing products