6 July 2026[1]
EMA/PRAC/124080/2026
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 June 2026 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 8-11 June 2026 (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 (22-25 June 2026) 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. Darolutamide – Angioedema

Authorisation procedure	Centralised
EPITT No	20237
PRAC Rapporteur	Jan Neuhauser (AT)
Date of adoption	11 June 2026

Recommendation

Having considered the available evidence in EudraVigilance, including the submitted cumulative review and additional data on time to onset, the PRAC has agreed that the MAH of Nubeqa (Bayer AG) 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

Table 1

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

Angioedema [g, h]

[g] Includes laryngeal oedema, lip swelling, swelling face, and swollen tongue

[h] Spontaneous reports from post-marketing experience

Package leaflet

4 Possible side effects

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- swelling under the skin in areas such as the face, lips, tongue and throat

1.2. Gemcitabine – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	20256
PRAC Rapporteur	Jenny Jönsson (SE)
Date of adoption	11 June 2026

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

Recommendation

Having considered all the available evidence, including data from EudraVigilance and the literature, including the comments received by the Marketing Authorisation Holder/s (MAH/s) of gemcitabine (CHEPLAPHARM ARZNEIMITTEL GMBH and SUN PHARMACEUTICAL INDUSTRIES EUROPE B.V.), the PRAC has agreed that the MAHs of all gemcitabine-containing medicinal 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, text to be deleted ~~strikethrough~~).

Considering 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

Severe cutaneous adverse reactions (SCARs)

~~Severe cutaneous adverse reactions (SCARs) including~~ Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment (see section 4.8). Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. ~~and monitored closely for skin reactions.~~ If signs and symptoms suggestive of these reactions appear, gemcitabine should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a severe cutaneous adverse reaction with the use of gemcitabine, treatment with gemcitabine must not be restarted at any time.

4.8 Undesirable effects

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders SOC: Frequency: Not known

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package leaflet

2. What you need to know before you take Gemcitabine

Warnings and precautions

Talk to your doctor before using gemcitabine if:

- you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after using gemcitabine.

~~Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP) have been reported in association with gemcitabine~~

~~treatment. Seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.~~

This medicine can cause serious skin reactions. Seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

You should contact your doctor immediately if you develop any of the following symptoms: (Note: Add the following heading, if the existing one differs and does not adequately reflect the urgency of the required action, ensuring it applies to all listed severe cutaneous adverse reactions: "Seek medical attention immediately if you notice any of the following symptoms of serious skin reactions:")

- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome) (frequency: not known).

1.3. Valproate and related substances[4] – Neurodevelopmental disorders with paternal exposure

Authorisation procedure	Non-centralised
EPITT No	20191
PRAC Rapporteur	Liana Martirosyan (NL)
Date of adoption	11 June 2026

Recommendation

Taking into account the available evidence in the literature, the PRAC considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk. The PRAC agreed to maintain the precautionary measures in the product information and additional risk minimisation measures. The final report of the PASS TANGO study will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies. However, an update on the information provided in the product information is necessary, as the current product information only describes the results of the paternal PASS whereas other available (epidemiological) studies have shown variable results. It is considered important to reflect this in the product information for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information, and to acknowledge the totality of available evidence on this potential risk. The aRMM should be updated in line with the proposed PI updates.

Therefore, the PRAC has agreed that the MAHs of valproate containing products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below taking into account the already existing wording in some nationally authorised products the text needs to be adapted by MAHs to individual products (new text underlined and in **bold** and deletions in ~~strikethrough~~):

Summary of product characteristics

4.4 Special warnings and precautions for use

Use in male patients

[4] Valproic acid, sodium valproate, valproate semisodium, valpromide

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. **However, other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, available evidence is inconsistent and the causal role of valproate is uncertain** (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

4.6 Fertility, pregnancy and lactation

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Package leaflet

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

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore it is not clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study has limitations and was not large enough to show which particular specific type of movement and mental developmental disorder children may be at risk of developing.~~

Other studies did not suggest an increased risk of mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Overall, it is not known whether any possible risk of childhood developmental disorders is caused by valproate itself or by other factors, such as the father's underlying medical condition.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

1.4. X-ray contrast agents: iobitridol; iodixanol; iohexol; iomeprol; iopamidol; iopromide; ioversol; ioxitalamic acid – Fixed drug eruption

Authorisation procedure	Non-centralised
EPITT No	20229
PRAC Rapporteur	Pernille Harg (NO)
Date of adoption	11 June 2026

Recommendation

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 MAHs of products containing iomeprol, iodixanol, ioversol, iopromide, iopamidol, iohexol, iobitridol and ioxitalamic acid should submit a variation within two 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

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

Fixed drug eruption

Package leaflet

4 Possible side effects

Under section side effects reported/described with frequency 'Not known' (frequency cannot be estimated from the available data)

An allergic skin reaction that may include round or oval patches of redness and swelling of the skin, blistering, and itching (fixed drug eruption). Darkening of the skin in affected areas, which might persist after healing, may also occur.

Fixed drug eruption usually reoccurs at the same site(s) if the medication is <taken> <used> again.

Taking into account the already existing wording in some nationally authorised products the text may need to be adapted by MAHs to individual products.

1.5. Zolbetuximab – Protein-losing gastroenteropathy

Authorisation procedure	Centralised
EPITT No	20236
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	11 June 2026

Recommendation

Having considered the available evidence in EudraVigilance and literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Vyloy, 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):

Summary of product characteristics

4.8 Undesirable effects

The following adverse reactions should be added under the SOC Gastrointestinal disorders:

Gastritis (frequency: uncommon)

Protein-losing gastroenteropathy (frequency: not known)

Package leaflet

4. Possible side effects

Other possible side effects:

Uncommon (may affect up to 1 in 100 people)

Inflammation of the stomach lining (gastritis)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

Loss of protein from the digestive tract (protein-losing gastroenteropathy)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Abemaciclib; palbociclib; ribociclib	Progressive multifocal leukoencephalopathy (PML) (20271)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 26 August 2026)	Eli Lilly Nederland B.V., Novartis Europharm Limited, Pfizer Europe MA EEIG
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab / relatlimab; pembrolizumab; retifanlimab; serplulimab; sugemalimab; tislelizumab; toripalimab; tremelimumab	Acquired haemophilia (20279)	Bianca Mulder (NL)	Supplementary information requested (submission by 26 August 2026)	Accord Healthcare S.L.U., AstraZeneca AB, Beone Medicines Ireland Limited, Bristol-Myers Squibb Pharma EEIG, Cstone Pharmaceuticals Ireland Limited, GlaxoSmithKline Trading Services Limited, Incyte Biosciences Distribution B.V., Merck Europe B.V., Merck Sharp & Dohme B.V., Regeneron Ireland Designated Activity Company (DAC), Roche Registration GmbH, Topalliance Biosciences Europe Limited
Belzutifan	Retinal oedema (20278)	Dennis Lex (DE)	Assess in the ongoing PSUR (submission by 5 August 2026 with the MAH comments to the PSUR preliminary assessment report)	Merck Sharp & Dohme B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cefpodoxime	Drug interaction between cefpodoxime and proton pump inhibitor (PPIs) resulting in a potentially reduced efficacy of cefpodoxime (20280)	Amelia Cupelli (IT)	Supplementary information requested (submission by 26 August 2026)	Teofarma, Scharper SpA, Zentiva France
Lithium	Drug interaction between lithium and GLP-1 agonists leading to increased lithium levels (20275)	Dennis Lex (DE)	Supplementary information requested (submission by 26 August 2026)	Teva, Laboratoires Delbert, Teofarma, Oba Pharma
Luspatercept	Ventilation perfusion mismatch (20281)	Jo Robays (BE)	Assess in the next PSUR (submission by 2 September 2026)	Bristol -Myers Squibb Pharma
Osimertinib	Pulmonary alveolar haemorrhage (20284)	Bianca Mulder (NL)	Assess in the next PSUR (submission by 10 February 2027)	AstraZeneca AB

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Vortioxetine	Acute pancreatitis (20234)	Jo Robays (BE)	Routine pharmacovigilance	MAHs of vortioxetine-containing products