20 August 2025[1]
EMA/PRAC/224799/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 7-10 July 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 7-10 July 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 (21-24 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. Ciltacabtagene autoleucel; idecabtagene vicleucel; tisagenlecleucel – Progressive multifocal leukoencephalopathy

Authorisation procedure	Centralised
EPITT No	20153
PRAC Rapporteur	Gabriele Maurer (DE)
Date of adoption	10 July 2025

Recommendation

Having considered the available evidence in EudraVigilance, including the cumulative review and responses to the list of questions submitted by the Marketing Authorisation Holders (MAHs), existing information on infections in SmPC section 4.8 and package leaflet section 4 for all three products, and the strategy in regulatory decision-making proposed by Segec et al (Clin Pharmacol Ther. 2015 Nov;98(5):502-5; doi: 10.1002/cpt.199) the PRAC has agreed that the MAHs of Abecma (Bristol-Myers Squibb Pharma EEIG), Carvykti (Janssen-Cilag International NV) and Kymriah (Novartis Europharm Limited) should submit a variation within 2 months from the publication of the PRAC recommendation to amend product information as described below (new text underlined, text to be deleted ~~strikethrough~~):

Kymriah

Summary of product characteristics

4.4 Special warnings and precautions for use
Serological testing

There is currently no experience with manufacturing Kymriah for patients testing positive for HBV, HCV and HIV.

Screening for HBV, HCV and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing. ~~Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure and death.~~

Viral reactivation

Hepatitis B virus (HBV) reactivation can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure and death.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with Kymriah who have also received prior treatment with other immunosuppressive medications. Cases with fatal outcome have been reported.

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

Abecma

Summary of product characteristics

4.4 Special warnings and precautions for use

Viral reactivation

[…]

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with Abecma who have also received prior treatment with other immunosuppressive medications.

Carvykti

Summary of product characteristics

4.4 Special warnings and precautions for use

Viral reactivation

[…]

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with CARVYKTI who have also received prior treatment with other immunosuppressive medications. Cases with fatal outcome have been reported.

1.2. Clozapine – New aspect of the known risk of neutropenia/agranulocytosis with potential impact on the risk minimisation measures

Authorisation procedure	Non-centralised
EPITT No	20141
PRAC Rapporteur	Amelia Cupelli (IT)
Date of adoption	10 July 2025

Recommendation *[see also section 3]*

Having considered the available evidence from EudraVigilance, from the literature, the DARWIN study reports[4] on real-world evidence data, as well as data provided by the innovator MAH for clozapine (Viatris Healthcare Limited), the PRAC has agreed that the current recommendations regarding blood monitoring to mitigate the risk of agranulocytosis should be revised according to the epidemiology and risk window for clozapine-related agranulocytosis; additionally, specific thresholds for the sub-population with benign ethnic neutropenia (BEN) should be indicated. MAHs of clozapine 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 to be added is underlined, text to be deleted is ~~struck through~~):

[4] DARWIN EU® - Clozapine and the incidence of agranulocytosis over time | HMA-EMA Catalogues of real-world data sources and studies

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

[…]

[Product name] can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of antipsychotic drug treatment,**
- **or with psychosis in Parkinson's disease when other treatment strategies have failed (see point 4.1)**
- **who have initially normal ~~leukocyte findings (white blood cell count ≥ 3500/mm^3(≥ 3.5x10^9/L), and ANC ≥ 2000/mm^3 (≥ 2.0x10^9/L)), and~~ neutrophil findings (Absolute Neutrophil Count; ANC) ≥1500/mm^3(1.5x10^9/L) in general population and ≥1000/mm^3(1.0x10^9/L) in patients with confirmed benign ethnic neutropenia (BEN), and**
- **in whom regular ~~white blood cell (WBC) counts and~~ absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, ~~and at least every 4 weeks thereafter throughout treatment~~ then monthly for the following 34 weeks (i.e., until the completion of the first year of treatment). After 12 months, if there has been no history of neutropenia during the first year, ANC monitoring should be reduced to once every 12 weeks. After 24 months, an ANC count should be collected once a year, provided there has been no history of neutropenia during the previous two years. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment. ANC count must be performed immediately if signs or symptoms of infection occur (e.g. fever, sore throat, mouth/throat ulcers). Additional ANC count should be considered in older patients, and after addition of valproic acid to clozapine, especially during the initiation period. ~~Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of [product name].~~ (see sections 4.4 and 4.5)**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving [product name] should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flulike complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

[Product name] must be dispensed under strict medical supervision in accordance with official recommendations.

[…]

4.2 Posology and method of administration

[…]

Initiation of [product name] treatment must be restricted to those patients with ~~a WBC count ≥ 3500/mm3 (3.5x10^9/L) and~~ an ANC ≥ 15~~20~~00/mm^3 (1.5~~2.0~~x10^9/L) within standardised normal limits.

[…]

4.4 Special warnings and special precautions for use

Agranulocytosis

[Product name] can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of ~~WBC counts and~~ ANC monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations. Because of the risks associated with [product name], its use is limited to patients in whom therapy is indicated as set out in section 4.1 (Therapeutic indications) and:

- who have initially normal ~~leukocyte findings (white blood cell count ≥ 3500/mm^3 (≥ 3.5x10^9/L), and ANC ≥ 2000/mm^3 (≥ 2.0x10^9/L)), and~~ neutrophil findings (Absolute Neutrophil Count; ANC) ≥1500/mm^3(1.5x10^9/L) in general population and ≥1000/mm^3(1.0x10^9/L) in patients with confirmed benign ethnic neutropenia (BEN), and
- in whom regular ~~WBC counts and~~ ANC can be performed weekly for the first 18 weeks, and ~~and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of [product name]~~ then monthly for the next 34 weeks. After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.

Before initiating clozapine therapy patients should have a blood test (see "agranulocytosis") and a history and physical examination. […]

Prescribing physicians should comply fully with the required safety measures.

Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.

Immediate discontinuation of [product name] is mandatory if ~~either the WBC count is less than 3000/mm^3 (3.0x10^9/L) or~~ the ANC is less than 10~~5~~00/mm^3 (1.0~~5~~x10^9/L) at any time during [product name] treatment.

Patients in whom [product name] has been discontinued as a result of ~~either WBC or~~ ANC deficiencies must not be re-exposed to [product name].

At each consultation, a patient receiving [product name] should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are

encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting [product name].

Patients with benign ethnic neutropenia (BEN) should be given special consideration and may be started on [product name] with the agreement of a haematologist (see section "Patients with Benign Ethnic Neutropenia (BEN)").

~~WBC counts and~~ ANC monitoring

~~WBC and d~~Differential blood counts must be performed within 10 days prior to initiating [product name] treatment to ensure that only patients with ~~normal WBC counts and ANC (WBC count ≥ 3500/mm^3 (3.5x10^9/L) and~~ ANC >~~20~~15$\underline{0}$0/mm^3 (1~~2~~.5~~0~~x10^9/L)) will receive the drug. After the start of [product name] treatment ~~the WBC count and~~ ANC must be monitored weekly for the first 18 weeks, and ~~at least at four-week intervals thereafter~~ then monthly for the next 34 weeks. After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.

Monitoring must continue throughout treatment as reported before, and for 4 weeks after complete discontinuation of [product name] or until haematological recovery has occurred (see below Low ~~WBC count~~/ANC). At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop.

~~WBC and d~~Differential blood counts must be performed immediately, if any symptoms or signs of an infection occur.

Low ~~WBC count~~/ANC

If, during [product name] therapy, ~~either the WBC count falls to between 3500/mm^3 (3.5x10^9/L) and 3000/mm^3 (3.0x10^9/L) or~~ the ANC falls to between ~~20~~15$\underline{0}$0/mm^3 (1~~2~~.5~~0~~x10^9/L) and ~~15~~1$\underline{0}$00/mm^3 (1.0~~1.5~~x10^9/L), haematological evaluations must be performed at least twice weekly until the patient's ~~WBC count and~~ ANC stabilises within the range ~~3000-3500/mm^3 (3.0-3.5x10^9/L) and~~ 1$\underline{0}$~~5~~00-15~~20~~00/mm^3 (1.$\underline{0}$~~5~~-1~~2~~.5~~0~~x10^9/L), respectively, or higher. After stabilisation and/or resolution, ANC monitoring must be performed monthly throughout treatment.

Immediate discontinuation of [product name] treatment is mandatory if ~~either the WBC count is less than 3000/mm^3 (3.0x10^9/L) or the~~ ANC is less than 1$\underline{0}$~~5~~00/mm^3 (1.$\underline{0}$~~5~~x10^9/L) during [product name] treatment.

~~WBC counts and d~~Differential blood counts should then be performed daily and patients should be

carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, [product name] should be discontinued after the first blood count.
Following discontinuation of [product name], haematological evaluation is required until haematological recovery has occurred.

Table 1. Actions to be taken with [product name] depending on ANC values for general population

Blood cell count		Action required
~~WBC/mm^3 (/L)~~	ANC/mm^3 (/L)	
~~≥ 3500 (≥3.5x10^9)~~	≥ 15~~20~~00 (≥1~~2~~.5~~0~~x10^9)	Continue [product name] treatment
~~3000-3500 (3.0x10^9-3.5x10^9)~~	10~~5~~00-15~~20~~00 (1.0~~5~~x10^9-1~~2~~.5~~0~~x10^9)	Continue [product name] treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.
~~<3000 (<3.0x10^9)~~	<10~~5~~00 (<1.0~~5~~x10^9)	Immediately stop [product name] treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If [product name] has been withdrawn and ~~either a further drop in~~ the ~~WBC count below 2000/mm^3 (2.0x10^9/L) occurs or the~~ ANC falls below 1000/mm3 (1.0x10^9/L), the management of this condition must be guided by an experienced haematologist.

Patients with Benign Ethnic Neutropenia (BEN)
In patients with confirmed BEN, the adjusted ANC threshold for starting or continuing clozapine is ANC ≥ 1000/mm^3 (1.0 × 10^9/ L). If the ANC is between 500 and 999/mm^3 (0.5–0.9×10^9/L), monitoring must be done twice weekly. Clozapine should be discontinued if the ANC falls below 500/mm^3 (0.5 × 10^9 /L).

Table 2. Actions to be taken with [product name] depending on ANC values for BEN patients

ANC/mm^3 (/L)	Action required
≥ 1000 (≥1.0x10^9)	Continue [product name] treatment
500-999 (0.5x10^9-0.9x10^9)	Continue [product name] treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.

<500 (<0.5x10^9)	Immediately stop [product name] treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Discontinuation of therapy for haematological reasons
Patients in whom [product name] has been discontinued as a result of ~~either WBC or~~ ANC deficiencie~~s~~ (see above) must not be re-exposed to [product name].

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged ~~in the future~~. Patients should be monitored weekly for 4 weeks in case of complete discontinuation.

Discontinuation of therapy for other reasons

Patients who have been on [product name] for more than ~~18 weeks~~ two years with no history of neutropenia and have had their treatment interrupted for causes different from neutropenia, do not need to resume the weekly monitoring schedule but the one used before the interruption, irrespective of the duration of interruption (i.e yearly controls). In case of complete discontinuation, those patients should not be monitored weekly for 4 weeks.

Patients who have been on [product name] between 18 weeks and 2 years or for more than 2 years with history of mild neutropenia that did not lead to treatment interruption, or patients who have had their treatment interrupted for more than 3 days but less than 4 weeks should have their ~~WBC count and~~ ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If [product name] treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section 4.2 Posology and method of administration). In case of complete discontinuation those patients should be monitored weekly for 4 weeks.

Table 3 below summarises the ANC monitoring after [product name] interruption.

Table 3. ANC monitoring upon resuming clozapine after treatment interruption for other reasons (not haematological)

Treatment duration before interruption	Neutropenia episodes before interruption	Interruption duration	Recommended ANC monitoring
≥ Two years	No	Irrelevant	Schedule used before the interruption (i.e yearly controls).
≥ Two years	Yes	3 days to <4 weeks	Weekly for 6 weeks. After that period, if no
> 18 weeks – Two years	Yes/No	3 days to <4 weeks	

			haematological abnormality occurs, monitor at intervals not exceeding 4 weeks.
≥ Two years	Yes	≥4 weeks	Weekly for the next 18 weeks of treatment, then monthly and dose should be re-titrated.
> 18 weeks – Two years	Yes/No	≥4 weeks	

Other precautions

[…]

Fever

During [product name] therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the ~~WBC~~ ANC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, [product name] should be discontinued immediately and appropriate medical measures should be administered.

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[…]

Other

[…]

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where [product name] was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Concomitant treatment of clozapine and valproic acid may increase the risk of neutropenia. If concomitant use of clozapine with valproic acid is necessary, careful monitoring is required.

[…]

4.8 Undesirable effects

[…]

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to [product name] treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the ~~WBC~~ ANC count is mandatory (see section 4.4).

[…]

Package leaflet

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

[…]

Medical check-ups and blood tests

Before you start taking [product name], your doctor will ask about your medical history and do a blood test to ensure that your white blood cells count is normal. It is important to find this out, as your body needs white blood cells to fight infections.

Make sure that you have regular blood tests before you start treatment, during treatment and after you stop treatment with [product name].

- Your doctor will tell you exactly when and where to have the tests. [Product name] may only be taken if you have a normal blood count.

- [Product name] can cause a serious decrease in the number of white cells in your blood (agranulocytosis). Only regular blood tests can tell the doctor if you are at risk of developing agranulocytosis (see section 4).

- During the first 18 weeks of treatment, blood tests are needed once a week. Afterwards, tests are needed at least once a month for the following 34 weeks.

- After 12 months of treatment, blood tests must be performed every 12 weeks for a year, and then yearly, if a decrease in the number of white cells in your blood is not detected.

- If there is a decrease in the number of white blood cells, you will have to stop [product name] treatment immediately. Your white blood cells should then return to normal.

- You will need to have blood tests for another 4 weeks after the end of [product name] treatment in case of complete discontinuation caused by haematological reasons (i.e. agranulocytosis) or in case of duration of monitoring < 2 years and/or in presence of history of neutropenia that had not led to treatment interruption.

[…]

1.3. Varicella vaccine (live); measles, mumps, rubella and varicella vaccine (live) – New aspect of the known risk of encephalitis

Authorisation procedure	Centralised and non-centralised
EPITT No	20180
PRAC Rapporteur	Jean-Michel Dogné (BE)
Date of adoption	10 July 2025

Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance including the cumulative reviews submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs of Varilrix and Priorix Tetra (GlaxoSmithKline Biologicals S.A.) and Varivax and Proquad (Merck Sharp & Dohme B.V.) should submit a variation as soon as possible and no later than 30 days from the publication of the PRAC recommendation to amend the product information as described below (new text underlined, deleted text ~~strikethrough~~):

1. Varilrix

Summary of product characteristics

4.4 Special warnings and precautions for use

Encephalitis

Encephalitis has been reported during post-marketing use of live attenuated varicella vaccines. In a few cases fatal outcomes have been observed, especially in patients who were immunocompromised (see section 4.3). Vaccinees/parents should be instructed to seek prompt medical attention if they/their child experience, after vaccination, symptoms suggestive of encephalitis such as loss or reduced levels of consciousness, convulsions or ataxia accompanied by fever and headache.

4.8 Undesirable effects

Post-marketing data

Nervous system disorders: encephalitis*****, cerebrovascular accident, seizure, cerebellitis, cerebellitis-like symptoms (including transient gait disturbance and transient ataxia)

* see description of selected adverse reactions.

Description of selected adverse reactions

Encephalitis has been observed following vaccination with live attenuated varicella vaccines. Fatal outcome was reported in a few cases, especially in immunocompromised people (see section 4.4).

Package leaflet

4 Possible side effects
The following side effects have been reported on a few occasions during routine use of Varilrix:

- Infection or inflammation of the brain (encephalitis) has been observed following vaccination with live attenuated varicella vaccines. In a few cases, this condition has been fatal, especially in people with weakened immune systems (as noted in section 2, Varilrix must not be used in patients with weakened immune systems). Seek immediate medical attention if you or your

child develop loss or reduced levels of consciousness, convulsions or loss of control of bodily movements, accompanied by fever and headache, as these might be a sign of infection or inflammation of the brain. Inform your doctor or pharmacist that you or your child received a live attenuated varicella vaccine.

- infection or inflammation of the ~~brain,~~ spinal cord and peripheral nerves resulting in temporary difficulty when walking (unsteadiness) and/or temporary loss of control of bodily movements~~, stroke (damage to the brain caused by an interruption to its blood supply)~~.
  ["stroke" should be presented in a separate bullet point]
- stroke (damage to the brain caused by an interruption to its blood supply).
- fits or seizures.
- shingles (herpes zoster).
- small spotted bleeding or bruising more easily than normal due to a drop in a type of blood cells called platelets.
- allergic reactions. Rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's surgery. However, if you or your child get any of these symptoms you should contact a doctor urgently.
- inflammation, narrowing or blockage of blood vessels. This may include unusual bleeding or bruising under the skin (Henoch Schonlein purpura) or fever which lasts for more than five days, associated with a rash on the trunk sometimes followed by a peeling of the skin on the hands and fingers, red eyes, lips, throat and tongue (Kawasaki disease).
- erythema multiforme (symptoms are red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body).

2. Varivax

Summary of product characteristics

4.4 Special warnings and precautions for use

Encephalitis

Encephalitis has been reported during post-marketing use of live attenuated varicella vaccines. In a few cases fatal outcomes have been observed, especially in patients who were immunocompromised (see section 4.3). Vaccinees/parents should be instructed to seek prompt medical attention if they/their child experience, after vaccination, symptoms suggestive of encephalitis such as loss or reduced levels of consciousness, convulsions or ataxia accompanied by fever and headache.

4.8 Undesirable effects

Post-Marketing Surveillance

Infections and infestations: Encephalitis*‡, Pharyngitis, Pneumonia*, Varicella (vaccine strain), Herpes zoster*‡, Aseptic meningitis‡

* These selected adverse events reported with varicella vaccine (live) (Oka/Merck strain) are also a consequence of wild-type varicella infection. There is no indication of an increased risk of these adverse events following vaccination compared with wild-type disease from active post-marketing surveillance studies or passive post-marketing surveillance reporting (see section 5.1).

‡ See section c.

c. Description of selected adverse reactions

Complications associated with varicella

Complications of varicella from vaccine strain, including herpes zoster and disseminated disease such as aseptic meningitis and encephalitis, have been reported in immunocompromised and immunocompetent individuals. A few cases of encephalitis with a fatal outcome have been observed following vaccination with live attenuated varicella vaccines, especially in immunocompromised people (see section 4.4).

Package leaflet

4 Possible side effects
Side effects that have been reported during marketed use of VARIVAX include:

- Infection or inflammation of the brain (encephalitis) has been observed following vaccination with live attenuated varicella vaccines. In a few cases, this condition has been fatal, especially in people with weakened immune systems (as noted in section 2, Varivax must not be used in patients with weakened immune systems). Seek immediate medical attention if you or your child develop loss or reduced levels of consciousness, convulsions or loss of control of bodily movements, accompanied by fever and headache, as these might be a sign of infection or inflammation of the brain. Inform your doctor or pharmacist that you or your child received a live attenuated varicella vaccine.
- illnesses affecting the nervous system (brain and/or spinal cord) such as sagging facial muscles and drooping eyelid on one side of the face (Bell's palsy), walking unsteadily, dizziness, tingling or numbness of the hands and feet, ~~inflammation of the brain (encephalitis),~~ inflammation of the coverings of the brain and spinal cord not caused by bacterial infection (aseptic meningitis), fainting
- shingles, sore throat (pharyngitis), purple or red-brown spots visible through the skin (Henoch-Schönlein purpura), secondary bacterial infections of the skin and soft tissues (including cellulitis), chickenpox (varicella), aplastic anaemia, which may include bruising or bleeding more easily than normal; red or purple, flat, pinhead spots under the skin; severe paleness

3. Priorix Tetra

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Encephalitis

Encephalitis has been reported during post-marketing use of live attenuated measles, mumps, rubella and varicella vaccines. In a few cases fatal outcomes have been observed, especially in patients who were immunocompromised (see section 4.3). Vaccinees/parents should be instructed to seek prompt medical attention if they/their child experience, after vaccination, symptoms suggestive of encephalitis such as loss or reduced levels of consciousness, convulsions or ataxia accompanied by fever and headache.

4.8 Undesirable effects

Post-marketing surveillance data

Nervous system disorders: encephalitis*±, cerebellitis, cerebrovascular accident, Guillain Barré syndrome, transverse myelitis, peripheral neuritis, cerebellitis like symptoms (including transient gait

disturbance and transient ataxia)

* These selected adverse events reported after vaccination are also a consequence of wild-type varicella infection. There is no indication of an increased risk of these adverse events following vaccination compared with wild-type disease.

+ see description of selected adverse reactions.

Description of selected adverse reactions

Encephalitis has been observed following vaccination with live attenuated measles, mumps, rubella and varicella vaccines. Fatal outcome was reported in a few cases, especially in immunocompromised people (see section 4.4).

Package leaflet

4 Possible side effects
The following side effects have been reported on a few occasions during routine use of GlaxoSmithKline Biologicals' measles, mumps, rubella or varicella vaccines:

- Infection or inflammation of the brain (encephalitis) has been observed following vaccination with live attenuated measles, mumps, rubella and varicella vaccines. In a few cases, this condition has been fatal, especially in people with weakened immune systems (as noted in section 2, Priorix Tetra must not be used in patients with weakened immune systems). Seek immediate medical attention if you or your child develop loss or reduced levels of consciousness, convulsions or loss of control of bodily movements, accompanied by fever and headache, as these might be a sign of infection or inflammation of the brain. Inform your doctor or pharmacist that you or your child received Priorix Tetra.
- infection or inflammation of the ~~brain,~~ spinal cord and peripheral nerves resulting in temporary difficulty when walking (unsteadiness) and/or temporary loss of control of bodily movements *["stroke" and "Guillain-Barré syndrome" should be presented in separate bullet points]*
- stroke
- inflammation of some nerves, possibly with pins and needles or loss of feeling or normal movement (Guillain-Barré syndrome)
- joint and muscle pain
- allergic reactions. Rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's surgery. However, if you get any of these symptoms you should contact a doctor urgently.
- narrowing or blockage of blood vessels
- punctual or small spotted bleeding or bruising more easily than normal due to a drop in platelets
- erythema multiforme (symptoms are red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body)
- chickenpox-like rash
- shingles (herpes zoster)
- measles and mumps like symptoms (including transient, painful swelling of the testicles and swollen glands in the neck)

4. Proquad

Summary of product characteristics

4.4 Special warnings and precautions for use

Encephalitis

Encephalitis has been reported during post-marketing use of live attenuated measles, mumps, rubella and varicella vaccines. In a few cases fatal outcomes have been observed, especially in patients who were immunocompromised (see section 4.3). Vaccinees/parents should be instructed to seek prompt medical attention if they/their child experience, after vaccination, symptoms suggestive of encephalitis such as loss or reduced levels of consciousness, convulsions or ataxia accompanied by fever and headache.

4.8 Undesirable effects

b. Tabulated list of adverse reactions

Infections and infestations: Aseptic meningitis*, Encephalitis*, Epididymitis, Herpes zoster*, Infection, Measles, Orchitis, Parotitis

* See section c.

c. Description of selected adverse reactions

Complications associated with varicella
Complications of varicella from vaccine strain including herpes zoster and disseminated disease such as aseptic meningitis and encephalitis have been reported in immunocompromised and immunocompetent individuals. A few cases of encephalitis with a fatal outcome have been observed following vaccination with live attenuated varicella vaccines, especially in immunocompromised people (see section 4.4).

Package leaflet

4 Possible side effects

Other side effects have been reported with the use of at least one of the following: ProQuad, previous formulations of monovalent and of the combined measles, mumps, and rubella vaccines manufactured by Merck Sharp & Dohme LLC, Rahway, NJ 07065, USA (herein after MSD), or Varicella Vaccine live (Oka/Merck). These adverse events include:

- Uncommon (may affect up to 1 in 100 people): cough.
- Rare (may affect up to 1 in 1,000 people): skin infection; chickenpox (varicella).
- Not known (frequency cannot be estimated from the available data):
    - Infection or inflammation of the brain (encephalitis) has been observed following vaccination with live attenuated measles, mumps, rubella and varicella vaccines. In a few cases, this condition has been fatal, especially in people with weakened immune systems (as noted in section 2, ProQuad must not be used in patients with weakened immune systems). Seek immediate medical attention if you or your child develop loss or reduced levels of consciousness, convulsions or loss of control of bodily movements, accompanied by fever and headache, as these might be a sign of infection or inflammation of the brain. Inform your doctor or pharmacist that you or your child received ProQuad.
    - unusual bleeding or bruising under the skin, swelling of the testicles; tingling of the

skin, herpes zoster (shingles); ~~inflammation of the brain (encephalitis)~~; inflammation of the coverings of the brain and spinal cord not caused by bacterial infection (aseptic meningitis), severe skin disorders; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); and inflammation of the lung (pneumonia/pneumonitis).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Bosutinib	Cutaneous vasculitis (20184)	Martin Huber (DE)	Supplementary information requested (submission by 27 August 2025)	Pfizer Europe MA EEIG
Datopotamab deruxtecan	Anaphylactic reaction (20181)	Mari Thörn (SE)	Supplementary information requested (submission by 27 August 2025)	Daiichi Sankyo Europe GmbH
Sulfasalazine	Idiopathic intracranial hypertension (pseudotumor cerebri) (20188)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 27 August 2025)	Pfizer
Valproate and related substances[5]	Neurodevelopmental disorders with paternal exposure (20191)	Liana Martirosyan (NL)	Supplementary information requested (submission by 24 September 2025)	Sanofi

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

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Clozapine	New aspect of the known risk of neutropenia/agranulocytosis with potential impact on the risk minimisation measures (20141)	Amelia Cupelli (IT)	· See section 1.2	MAHs of clozapine containing products
			· Distribute a joint direct healthcare communication (DHPC) according to the text and communication plan agreed with the PRAC	MAHs of clozapine containing products under the coordination of Viatris Healthcare Limited
Varicella vaccine (live); measles, mumps, rubella and varicella vaccine (live)	New aspect of the known risk of encephalitis (20180)	Jean-Michel Dogné (BE)	. See section 1.3	GlaxoSmithKline Biologicals S.A., Merck Sharp & Dohme B.V.
			· Discuss in PSURs any new information regarding encephalitis	GlaxoSmithKline Biologicals S.A., Merck Sharp & Dohme B.V.