



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 23-26 November 2020 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 23-26 November 2020 (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 (7-10 December 2020) 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.



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 information³

1.1. Capecitabine – Anaphylactic reaction

Authorisation procedure	Centralised and non-centralised
EPITT No	19561
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	26 November 2020

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the association of capecitabine with angioedema, the PRAC has agreed that the MAH(s) of capecitabine-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Summary of related ADRs reported in patients treated with capecitabine monotherapy

Immune system disorders

Frequency "rare": Angioedema (rare)

Package leaflet

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking <product name> immediately and contact your doctor if any of these symptoms occur:

- [...]
- **Angioedema:** Seek medical attention straight away if you notice any of the following symptoms - you may need urgent medical treatment: swelling mainly of the face, lips, tongue or throat which makes it difficult to swallow or breathe, itching and rashes. This could be a sign of angioedema.

[...]

Other side effects are:

[...]

Rare side effects (may affect up to 1 in 1,000 people) include:

- Angioedema (swelling mainly of the face, lip, tongue or throat, itching and rashes)

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. Chloroquine; hydroxychloroquine – Psychiatric disorders

Authorisation procedure	Non-centralised
EPITT No	19572
PRAC rapporteur(s)	Anette Kirstine Stark (DK)
Date of adoption	26 November 2020

Recommendation

Based on the review of the data on the risk of psychiatric disorders with chloroquine (CQ) or hydroxychloroquine (HCQ), additional information about the risk of these events was identified. For both substances, it was observed that psychiatric reactions occurred in patients with and without history of psychiatric disorders. In addition, cases have been reported for HCQ, indicating that psychiatric reactions could occur shortly after starting treatment. For CQ, data are insufficient to assess time to onset. Therefore, the PRAC concluded on the need to update the product information of CQ and HCQ-containing products with a more complete description of psychiatric adverse reactions and to strengthen the recommendations for healthcare professionals and patients. The proposed update is the minimum information to be included and should be adapted to any current information in the PI regarding suicidal behavior / suicide and psychiatric disorders / reactions.

The MAH(s) of chloroquine and hydroxychloroquine-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text underlined and **bold**, text to be removed ~~struck through~~):

Hydroxychloroquine

Summary of product characteristics (SmPC)

4.4. Special warnings and precautions for use

Suicidal behavior and psychiatric disorders

Suicidal behavior **and psychiatric disorders have** been reported in ~~very rare cases in~~ **some** patients treated with hydroxychloroquine (see section 4.8). **Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine and have been reported also in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.**

4.8. Undesirable effects

SOC: Psychiatric disorders

Common: Affect lability

Uncommon: Nervousness

Not known: suicidal behaviour, psychosis, **depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.**

Package leaflet (PL)

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

Some people being treated with [product name] can experience mental health problems such as irrational thoughts, anxiety, hallucinations, feeling confused or feeling depressed,

including thoughts of self-harm or suicide, even those who have never had similar problems before. If you or others around you notice any of these side effects (see section 4) seek medical advice straight away.

4. Possible side effects

Not known: Feeling depressed or having thoughts of self-harm or suicide, hallucinations, feeling nervous or anxious, feeling confused, agitated, difficulty sleeping, feeling elated or overexcited.

Chloroquine

Summary of product characteristics (SmPC)

4.4. Special warnings and precautions for use

Suicidal behaviour and psychiatric disorders

Cases of suicidal behaviour and psychiatric disorders have been reported in patients treated with chloroquine (see section 4.8), including in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

4.8. Undesirable effects

SOC: Psychiatric disorders

Very common: insomnia

Common: depression

Rare: psychiatric disorders such as anxiety, agitation, confusion, hallucinations, delirium

Not known: suicidal behaviour, **psychosis, aggression, delusion, paranoia, mania, attention deficit, sleep disorders.**

Package leaflet (PL)

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

Some people being treated with [product name] can experience mental health problems such as irrational thoughts, hallucinations, feeling confused, aggressiveness, paranoia, feeling depressed or have thoughts of self-harm or suicide, even those who have never had similar problems before. If you or others around you notice any of these side effects (see section 4) seek medical advice straight away.

4. Possible side effects

Not known: feeling depressed or having thoughts of self-harm or suicide, feeling anxious, feeling confused, having irrational thoughts, paranoia, aggressiveness, sleep disorders, agitation, feeling elated or overexcited, lack of concentration.

1.3. Pembrolizumab – Vasculitis

Authorisation procedure	Centralised
EPITT No	19578
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	26 November 2020

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the association of pembrolizumab with vasculitis, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of Keytruda (Merck Sharp & Dohme B.V.), should submit a variation within 2 months, to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

The following additional clinically significant, immune-related adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, ~~and~~ myelitis and vasculitis (see sections 4.2 and 4.8).

4.8. Undesirable effects

Tabulated list of adverse reactions

Table 2: Adverse reactions in patients treated with pembrolizumab

	Monotherapy	Combination with chemotherapy	Combination with axitinib
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
<u>Uncommon</u>		<u>vasculitis</u>	
<u>Rare</u>	<u>vasculitis</u>		

Package leaflet

4. Possible side effects

The following side effects have been reported with pembrolizumab alone:

Rare (may affect up to 1 in 1,000 people)

- inflammation of the blood vessels

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Uncommon (may affect up to 1 in 100 people)

- inflammation of the blood vessels

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azathioprine	Erythema nodosum (19623)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 4 February 2021)	Aspen Pharma, Novartis-Sandoz, Teva
Methotrexate	Progressive multifocal leukoencephalopathy (PML) (18473)	Martin Huber (DE)	Supplementary information requested (submission by 4 February 2021)	MAHs for methotrexate-containing products who have at least one case of PML in their database

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Teriparatide	Myeloma (19511)	Adrien Inoubli (FR)	Routine pharmacovigilance / Monitor in PSUR	MAHs of teriparatide-containing products
			Provide a study protocol on the IBM MarketScan database	Lilly