30 September 2024[1]
EMA/PRAC/373353/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 2-5 September 2024 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 2-5 September 2024 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (16-19 September 2024) 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. Medroxyprogesterone acetate (MPA) – Meningioma

Authorisation procedure	Non-centralised
EPITT No	20030
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	5 September 2024

Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance and literature, including the cumulative review submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs of all injectable formulations and ≥100 mg oral formulations containing medroxyprogesterone acetate 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):

Summary of product characteristics

4.3 Contraindications

MPA containing products with non-oncological indications (all injectable formulations and ≥100 mg oral formulations):

Meningioma or history of meningioma.

MPA containing products with both non-oncological and oncological indications (all injectable formulations and ≥100 mg oral formulations), the wording should be as follows:

Meningioma or history of meningioma (for non-oncological indications).

4.4 Special warnings and precautions for use

MPA containing products with non-oncological indications (all injectable formulations and ≥100 mg oral formulations):

Meningioma

Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients treated with medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice. If a patient is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure.
In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate.

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

MPA containing products for oncological indications (all injectable formulations and ≥100 mg oral formulations):

Meningioma

Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, the need for further treatment with medroxyprogesterone acetate should be carefully considered on a case-by-case basis taking into account individual benefits and risks. In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate.

MPA containing products which have both non-oncological and oncological indications (all injectable formulations and ≥100 mg oral formulations), the wording should be as follows:
Meningioma

Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). Patients treated with medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice.

In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate. If a patient treated for a non-oncological indication is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure.

If a patient treated for an oncological indication is diagnosed with meningioma, the need for further treatment with medroxyprogesterone acetate should be carefully considered on a case-by-case basis taking into account individual benefits and risks.

4.8 Undesirable effects

MPA containing products for all injectable formulations and ≥100 mg oral formulations:

SOC Neoplasms benign, malignant and unspecified: meningioma, frequency "not known".

5.1 Pharmacodynamic properties

MPA containing products for all injectable formulations and ≥100 mg oral formulations:

Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French National health data system (SNDS – Système National des Données de Santé) and included a population of 18, 061 women who had intracranial surgery for meningioma and 90, 305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3ml injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 ml (9/18 061 (0.05%) v 11/90 305 (0.01%), OR 5.55 (95%CI 2.27 to 13.56)). This excess risk seems to be driven primarily by prolonged use (≥3 years) of medroxyprogesterone acetate.

Package leaflet

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

MPA containing products with non-oncological indications (all injectable formulations and ≥100 mg oral formulations):

Do not use <product name>

If you have meningioma or have ever been diagnosed with a meningioma (a usually benign tumour of the tissue layer surrounding the brain and spinal cord).

Tell your doctor if any of the following conditions apply to you.

Subsection "warnings and precautions"

Meningioma

Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with <product name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

MPA containing products with oncological indications (all injectable formulations and ≥100 mg oral formulations):

Subsection "warnings and precautions"

Meningioma

Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will reconsider your treatment with <product name>. If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

MPA containing products which have both non-oncological and oncological indications (all injectable formulations and ≥100 mg oral formulations), the wording should be as follow:

Do not use <product name>

If you have meningioma or have ever been diagnosed with a meningioma (usually benign tumour of the tissue surrounding the brain and spinal cord) unless you use <product name> for cancer.

Tell your doctor if any of the following conditions apply to you.

Subsection "Warnings and precautions"

Meningioma

Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will reconsider your treatment with <product name>. If you notice any symptoms such as changes in

vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

4. Possible side effects

MPA containing products for all injectable formulations and ≥100 mg oral formulations

Usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma) with a frequency not known (see section 2 "Warnings and precautions").

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin, metformin; empagliflozin; empagliflozin, metformin; empagliflozin, linagliptin; ertugliflozin; ertugliflozin, metformin; ertugliflozin, sitagliptin; saxagliptin, dapagliflozin	Sarcopenia (20111)	Mari Thörn (SE)	Supplementary information requested (submission by 4 November 2024)	AstraZeneca AB, Janssen-Cilag International NV, Boehringer Ingelheim International GmbH, Merck Sharp & Dohme B.V.
Lenvatinib	Tumour lysis syndrome (20108)	Mari Thörn (SE)	Supplementary information requested (submission by 30 October 2024)	Eisai GmbH
Lisocabtagene maraleucel	Progressive multifocal leukoencephalopathy (20109)	Gabriele Maurer (DE)	Assess in the next PSUR (submission by 13 October 2024)	Bristol-Myers Squibb Pharma EEIG
Sacubitril, valsartan	Myoclonus (20097)	Karin Erneholm (DK)	Assess in the next PSUR (submission by 9 October 2024)	Novartis Europharm Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Medroxyprogesterone acetate (MPA)	Meningioma (20030)	Bianca Mulder (NL)	· See section 1.1	· MAHs of all injectable formulations and ≥100 mg oral formulations
			· Distribute a Direct Healthcare Professional Communication (DHPC)	· Pfizer Limited
			· Implement a targeted follow-up questionnaire	· MAHs of low dose oral formulations (<100 mg) and combination products containing MPA