



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 23-26 October 2023 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 October 2023 (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 (6-9 November 2023) 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. Dapagliflozin; dapagliflozin, metformin; dapagliflozin, saxagliptin – Acquired phimosis and phimosis

Authorisation procedure	Centralised and non-centralised
EPITT No	19935
PRAC Rapporteur	Mari Thörn (SE)
Date of adoption	26 October 2023

Recommendation

Having considered the available evidence in EudraVigilance, literature and the MAH's responses, the PRAC has agreed that the MAHs for dapagliflozin 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 underlined):

For dapagliflozin monoproducts

Summary of product characteristics

4.8 – Undesirable effects

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

<...>

In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

Cases of phimosis/acquired phimosis have been reported concurrent with genital infections and in some cases, circumcision was required.

For dapagliflozin and metformin combination products

Summary of product characteristics

4.8 – Undesirable effects

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more

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

frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Cases of phimosis/acquired phimosis have been reported with dapagliflozin concurrent with genital infections and in some cases, circumcision was required.

For dapagliflozin and saxagliptin combination products

Summary of product characteristics

4.8 – Undesirable effects

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

Saxagliptin/dapagliflozin combination: The reported adverse events of vulvovaginitis, balanitis and related genital infections from pooled safety analysis were reflective of the safety profile of dapagliflozin. Adverse events of genital infection were reported in 3.0% in the saxagliptin plus dapagliflozin plus metformin group, 0.9% of saxagliptin plus metformin group and 5.9% of subjects in the dapagliflozin plus metformin group. The majority of the genital infection adverse events were reported in females (84% of subjects with a genital infection), were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Cases of phimosis/acquired phimosis have been reported with dapagliflozin concurrent with genital infections and in some cases, circumcision was required.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Elasomeran (COVID-19 mRNA vaccine) - Spikevax	Postmenopausal haemorrhage (20015)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 3 January 2024)	Moderna Biotech Spain, S.L.
Esomeprazole; omeprazole	Erectile dysfunction (19976)	Rugile Pilviniene (LT)	Assess sexual dysfunction in the next PSUR (submission by 8 June 2024 for esomeprazole; by 14 July 2027 for omeprazole)	AstraZeneca AB and all MAHs eligible to submit PSURs as per the EURD list requirements

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Osimertinib	Progressive multifocal leukoencephalopathy (19984)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 10 February 2024)	AstraZeneca AB
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Postmenopausal haemorrhage (19989)	Menno van der Elst (NL)	Supplementary information requested (submission by 3 January 2024)	BioNTech Manufacturing GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amivantamab	Anaphylactic reaction (19928)	Gabriele Maurer (DE)	Monitor in PSURs	Janssen-Cilag International N.V.
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Thyroid cancer (18292)	Mari Thörn (SE)	Routine pharmacovigilance	Novo Nordisk A/S, AstraZeneca AB, Eli Lilly Nederland B.V., Sanofi Winthrop Industrie