



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

Adopted at the 13-16 March 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 13-16 March 2023 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>2</sup> 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 (27-30 March 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.

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<sup>1</sup> Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

<sup>2</sup> 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 information<sup>3</sup>

## 1.1. Propofol – Medication errors that could potentially lead to life-threatening/fatal cases

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19851
<b>PRAC Rapporteur</b>	Pernille Harg (NO)
<b>Date of adoption</b>	16 March 2023

### Recommendation

Having considered the available evidence in EudraVigilance, literature and the responses of the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs for propofol 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):

#### Outer and immediate packaging

“For single use in one patient. Risk of sepsis in multiple use”

“Use immediately after opening”

In case of insufficient space on the immediate packaging, the National Competent Authorities may decide to omit parts of the warning on the immediate packaging.

Font, size and colour of the text is to be decided at national level.

## 1.2. Voriconazole; flucloxacillin – Drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels

<b>Authorisation procedure</b>	Centralised and non-centralised
<b>EPITT No</b>	19849
<b>PRAC Rapporteur</b>	Liana Gross-Martirosyan (NL)
<b>Date of adoption</b>	16 March 2023

### Recommendation

Having considered the evidence from the literature, and the responses from the MAH for Vfend, the PRAC has agreed that the MAHs for voriconazole- and flucloxacillin-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):

#### Voriconazole-containing products

#### Summary of product characteristics

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

#### 4.5 Interaction with other medicinal products and other forms of interaction

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
...		
<u>Flucloxacillin</u> <u>[CYP450 inducer]</u>	<u>Significantly decreased plasma voriconazole concentrations have been reported.</u>	<u>If concomitant administration of voriconazole with flucloxacillin cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.</u>

#### Package leaflet

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

Other medicines and <product>

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/or <product> are still having the desired effect:

- ...
- Flucloxacillin (antibiotic used against bacterial infections)

The PRAC has also agreed that the MAHs should use the next appropriate regulatory procedure to revise section 4.5 of the SmPC to improve its readability (e.g., to sort the medicinal products in the first column of the table alphabetically per group of medicines).

#### Flucloxacillin-containing products

##### Summary of product characteristics

#### 4.5 Interaction with other medicinal products and other forms of interaction

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

#### Package leaflet

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

Other medicines and <product>

Tell your doctor or pharmacist before taking this medicine if you are taking any other medicines:

- ...
- Voriconazole (used against fungal infections)

## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ceftriaxone	Factor V inhibition (19853)	Zane Neikena (LV)	Assess in the next PSUR (submission by 24 August 2023)	MAHs of ceftriaxone-containing medicinal products
Dupilumab	Weight decreased, abnormal loss of weight, cachexia, body mass index decreased (19897)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 6 June 2023)	Sanofi Winthrop Industrie
Nusinersen	Arachnoiditis (19896)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 8 August 2023)	Biogen Netherlands B.V.
Olaparib	Hepatocellular damage and hepatitis (19846)	Amelia Cupelli (IT)	Supplementary information requested (submission by 5 May 2023)	AstraZeneca AB

## 3. Other recommendations

Not applicable