23 October 2023[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 25-28 September 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 25-28 September 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 (9-12 October 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.

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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. Azacitidine – Cutaneous vasculitis

Authorisation procedure	Centralised
EPITT No	19929
PRAC Rapporteur	Menno van der Elst (NL)
Date of adoption	28 September 2023

Recommendation *[see also section 3 for oral formulations]*

Having considered the available evidence in EudraVigilance and literature, the PRAC has agreed that a causal relationship between azacitidine injectable formulations and cutaneous vasculitis is at least a reasonable possibility. Therefore the Marketing Authorisation Holders (MAH) for azacitidine containing medicinal products (intravenous use and subcutaneous use only) 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):

Summary of product characteristics

4.8 – Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'not known': Cutaneous vasculitis

Package leaflet

4 - Possible side effects

Not known (frequency cannot be estimated from the available data)

Inflammation of blood vessels in the skin which may result in rash (cutaneous vasculitis)

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

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Abemaciclib; palbociclib; ribociclib	Erythema multiforme (19973)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 6 December 2023)	Eli Lilly Nederland B.V., Pfizer Europe MA EEIG, Novartis Europharm Limited
Chlorhexidine[4] and other relevant fixed-dose combinations[5]	Persistent corneal injury and significant visual impairment (19970)	Lina Seibokiene (LT)	Supplementary information requested (submission by 6 December 2023)	Becton Dickinson France, 3M Deutschland GmbH, Mölnlycke Health Care
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; insulin glargine, lixisenatide; lixisenatide; semaglutide; tirzepatide	Aspiration and pneumonia aspiration (19974)	Mari Thörn (SE)	Supplementary information requested (submission by 6 December 2023)	AstraZeneca AB, Eli Lilly Nederland B.V., Novo Nordisk A/S, Sanofi Winthrop Industrie

[4] For cutaneous use only

[5] Chlorhexidine, chlorocresol, hexamidine; chlorhexidine gluconate, chlorocresol, hexamidine; chlorocresol, hexamidine, chlorhexidine digluconate; benzalkonium chloride, chlorhexidine gluconate; chlorhexidine gluconate, benzoxonium chloride, retinol; benzalkonium chloride, chlorhexidine gluconate, benzyl alcohol; chlorhexidine gluconate; chlorhexidine gluconate, cetrimonium; chlorhexidine gluconate, chlorocresol, hexamidine; chlorhexidine gluconate, dexpanthenol; chlorhexidine gluconate, hydrocortisone; chlorhexidine gluconate, hydrogen peroxide, isopropyl alcohol; chlorhexidine gluconate, isopropyl alcohol; chlorhexidine gluconate, ethanol; chlorhexidine gluconate, phenol; benzalkonium chloride, chlorhexidine gluconate; benzalkonium chloride, chlorhexidine digluconate; chlorhexidine digluconate; chlorhexidine digluconate, ethanol; chlorhexidine digluconate, isopropyl alcohol; chlorhexidine dihydrochloride; benzalkonium chloride, chlorhexidine dihydrochloride, isopropyl myristate, liquid paraffin; chlorhexidine dihydrochloride, dexpanthenol; chlorhexidine dihydrochloride, nystatin; chlorhexidine dihydrochloride, nystatin, dexamethasone; chlorhexidine dihydrochloride, nystatin, hydrocortisone; chlorhexidine dihydrochloride, zinc oxide, pramocaine hydrochloride;, triamcinolone acetonide; chlorhexidine dihydrochloride, dexpanthenol, alphatocopherol acetate, vitamin A; chlorhexidine gluconate; cetrimide, chlorhexidine digluconate; chlorhexidine acetate; cetrimide, chlorhexidine acetate; retinol palmitate, chlorhexidine acetate; retinol palmitate, benzocaine, retinol, chlorhexidine acetate; bacitracin zinc, chlorhexidine acetate; nystatin, hydrocortisone, chlorhexidine acetate.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Teriparatide	Alopecias (19972)	Tiphaine Vaillant (FR)	Supplementary information requested (submission by 6 December 2023)	MAHs of teriparatide with the obligation to submit PSURs

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azacitidine (oral formulations)	Cutaneous vasculitis (19929)	Menno van der Elst (NL)	Routine pharmacovigilance (see section 1.1 for injectable formulations)	Bristol-Myers Squibb Pharma EEIG
Baricitinib	Interstitial lung disease (19880)	Adam Przybylkowski (PL)	Routine pharmacovigilance	Eli Lilly Nederland B.V.
Chlorhexidine gluconate, isopropyl alcohol; chlorhexidine digluconate, isopropyl alcohol	Product caught fire (19969)	Jo Robays (BE)	Routine pharmacovigilance	MAHs of chlorhexidine (di)gluconate/isopropyl alcohol-containing medicinal products
Rituximab	Oral lichenoid reaction (19916)	Karin Susanne Erneholm (DK)	Routine pharmacovigilance	MAHs of rituximab-containing medicinal products