8 February 2021[1]
EMA/PRAC/19647/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 11-14 January 2021 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 11-14 January 2021 (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 (25-29 January 2021) 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. Adalimumab – Abnormal weight gain

Authorisation procedure	Centralised
EPITT No	19520
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	14 January 2021

Recommendation

Having considered the available evidence in EudraVigilance and the literature, as well the data from clinical trials in the cumulative review provided by the MAH of Humira (AbbVie), the PRAC has agreed that the MAH(s) of adalimumab - 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):

Summary of product characteristics

4.8. Undesirable effects

Investigations

Frequency 'Not known': Weight increased[2)]

2) The mean weight change from baseline for adalimumab ranged from 0.3 kg to 1.0 kg across adult indications compared to (minus) -0.4 kg to 0.4 kg for placebo over a treatment period of 4-6 months. Weight increase of 5-6 kg has also been observed in long-term extension studies with mean exposures of approximately 1-2 years without control group, particularly in patients with Crohn's disease and ulcerative colitis. The mechanism behind this effect is unclear but could be associated with the anti-inflammatory effect of adalimumab.

Package leaflet

4. Possible side effects

Not known (frequency cannot be estimated from available data)

[…]

- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).
- weight gain (for most patients, the weight gain was small)

[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. Anastrozole – Depressed mood disorders

Authorisation procedure	Non-centralised
EPITT No	19592
PRAC rapporteur(s)	Zane Neikena (LV)
Date of adoption	14 January 2021

Recommendation

Having considered the available evidence from EudraVigilance and Lareb databases, literature, cumulative review, including clinical trial data, provided by the MAH of the innovator Arimidex (AstraZeneca) and the biological plausibility for a possible association of anastrozole with depression the PRAC has agreed that the MAH(s) of anastrozole-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):

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

[...]

SOC Psychiatric disorders

Frequency 'Very common': Depression

Package leaflet

4 - Possible side effects

[…]

Very common side effects (affect more than 1 in 10 people)

[…]

Depression

1.3. Hydrocortisone – Adrenal crisis

Authorisation procedure	Centralised
EPITT No	19656
PRAC rapporteur(s)	Annika Folin (SE)
Date of adoption	14 January 2021

Recommendation *[see also section 3]*

Having considered the available evidence, following the assessment of the data and literature obtained from the Marketing Authorisation Holder (MAH) of Alkindi (Diurnal Europe BV), the PRAC has agreed the following recommendation:

1. A Direct Healthcare Professional Communication (DHPC) and Communication plan for the risk of acute adrenal insufficiency when switching from crushed or compounded oral hydrocortisone formulations to Alkindi hydrocortisone granules in capsules for opening, were agreed by the PRAC. The MAH of Alkindi should distribute a DHPC according to the text and communication plan agreed with the CHMP.

2. The product information for Alkindi (hydrocortisone granules in capsules for opening) should be updated to reflect the risk of acute adrenal insufficiency when switching from crushed or compounded oral hydrocortisone formulations to Alkindi hydrocortisone granules in capsules for opening. The MAH of Alkindi should submit a variation within two months to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~).

[…]

Summary of product characteristics

4.2. Posology and method of administration

Changing from conventional oral glucocorticoid treatment to Alkindi

When changing patients from conventional oral hydrocortisone replacement therapy, crushed or compounded, to Alkindi, an identical total daily dose may be given. Alkindi is therapeutically equivalent to conventional oral hydrocortisone ~~tablets~~ formulations. Where a patient is changed from other oral hydrocortisone formulations to Alkindi, inaccuracy in the dosing possible with other oral hydrocortisone formulations can lead to a relative fall in hydrocortisone exposure on the same nominal dose, leading to symptoms of adrenal insufficiency or crisis (see section 4.4).

4.4. Special warnings and precautions for use

Adrenal crisis

[…]

Adrenal crisis can occur when switching from conventional oral hydrocortisone formulations, crushed or compounded, to Alkindi. Close monitoring of patients is recommended in the first week after switch. Healthcare professionals should inform carers and patients that extra doses of Alkindi should be given if symptoms of adrenal insufficiency are seen. If this is required, then an increase in the total daily dose of Alkindi should be considered and immediate medical advice should be sought.

Package leaflet

2 - What you need to know before you give Alkindi

Warnings and precautions

- When your child is changing to Alkindi from another hydrocortisone preparation.

Differences between hydrocortisone preparations when changing to Alkindi may mean your child could be at risk of receiving an incorrect dose of hydrocortisone in the first week after switching to Alkindi. This may lead to a risk of adrenal crisis. You should watch your child carefully in the week after changing to Alkindi and give extra doses of Alkindi if there are symptoms of adrenal crisis such as unusual tiredness, headache, a raised or low temperature or vomiting. If this happens medical attention should be sought right away.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Alemtuzumab	Sarcoidosis (19638)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 3 March 2021)	Sanofi Belgium
Clindamycin	Acute renal failure (19647)	Sonja Hrabcik (AT)	Supplementary information requested (submission by 3 March 2021)	Pfizer
Eliglustat	Erectile dysfunction (19644)	Eva A. Segovia (ES)	Supplementary information requested (submission by 3 March 2021)	Genzyme Europe BV
Labetalol	Nipple pain and suppressed lactation (19639)	Pernille Harg (NO)	Supplementary information requested (submission by 3 March 2021)	Aspen Pharma
Rituximab	Sarcoidosis (19642)	Hans Christian Siersted (DK)	Assess in the ongoing PSUSA (submission of response by 11 February 2021)	Roche Registration GmbH
Romosozumab	Cardiac arrhythmia (19629)	Adrien Inoubli (FR)	Supplementary information requested (submission by 3 March 2021)	UCB Pharma S.A.
Secukinumab	Facial paralysis (19653)	Eva A. Segovia (ES)	Assess in the next PSUR (submission by 5 March 2021)	Novartis Europharm Limited
Secukinumab	Henoch-Schonlein purpura (19640)	Eva A. Segovia (ES)	Supplementary information requested (submission by 3 March 2021)	Novartis Europharm Limited
Sulfamethoxazole, trimethoprim (co-trimoxazole)	Acute respiratory distress syndrome (19625)	Nikica Mirošević Skvrce (HR)	Supplementary information requested (submission by 3 March 2021)	Roche, Eumedica Pharmaceuticals, Aspen Pharma, Teva
Sulfamethoxazole, trimethoprim (co-trimoxazole)	Haemophagocytic lymphohistiocytosis (19655)	Nikica Mirošević Skvrce (HR)	Supplementary information requested (submission by 3 March 2021)	Roche, Eumedica Pharmaceuticals, Aspen Pharma, Teva

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Tramadol	Serotonin syndrome (19635)	Tiphaine Vaillant (FR)	Supplementary information requested (submission by 3 March 2021)	All MAHs for tramadol as single ingredient with the obligation to submit PSURs (The version of the EURD list published on 14 January 2021 should be used to determine the submission.)
Warfarin	Anticoagulant-related nephropathy (19652)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 3 March 2021)	Bristol-Myers Squibb

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Hydrocortisone	Adrenal crisis (19656)	Annika Folin (SE)	· See section 1.3 · Distribute a Direct Healthcare Professional Communication (DHPC) according to the text and communication plan agreed with the CHMP	Diurnal Europe BV
Pembrolizumab	Systemic scleroderma (19591)	Menno van der Elst (NL)	Routine pharmacovigilance	Merck Sharp & Dohme B.V.