11 February 2019[1]
EMA/PRAC/905027/2019 Corr[2]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 14-17 January 2019 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 14-17 January 2019 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][3] 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 (28-31 January 2019) 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.

[1] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The timeline to submit the variation for gabapentin-containing products was added on 12 February 2019 (see page 4).
[3] The relevant EPITT reference number should be used in any communication related to a signal.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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.

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[4]

1.1. Biotin – Interference with clinical laboratory tests

Authorisation procedure	Non-centralised
EPITT No	19156
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	17 January 2019

Recommendation *[see also section 3]*

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), as well as the MAHs' additional information, the PRAC considered there is sufficient evidence to support a potential interference with clinical laboratory tests of medicinal products for oral use containing ≥150 microgram biotin per dose unit and medicinal products for parenteral use containing ≥60 microgram biotin per dose unit. Therefore, the PRAC has agreed that the MAHs of medicinal products for oral use containing ≥150 microgram biotin per dose unit and medicinal products for parenteral use containing ≥60 microgram biotin per dose unit are to submit a variation within 3 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Interference with clinical laboratory tests

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results, depending on the assay. The risk of interference is higher in children and patients with renal impairment and increases with higher doses. When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed (e.g. thyroid test results mimicking Graves' disease in asymptomatic patients taking biotin or false negative troponin test results in patients with myocardial infarction taking biotin). Alternative tests not susceptible to biotin interference should be used, if available, in cases where interference is suspected. The laboratory personnel should be consulted when ordering laboratory tests in patients taking biotin.

Package leaflet

2. What you need to know before you take X

Warnings and precautions

[Product name] contains <quantity> biotin per <dose unit>. If you are about to undergo laboratory testing you must tell your doctor or the laboratory personnel that you are taking or have recently taken [Product name], because biotin may affect results of such tests. Depending on the test, the results may be falsely elevated or falsely low due to biotin. Your doctor may ask you to stop taking

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

[Product name] before performing laboratory tests. You should also be aware that other products that you may take, such as multivitamins or supplements for hair, skin, and nails could also contain biotin and affect the results of laboratory tests. Please inform your doctor or the laboratory personnel, if you are taking such products.

1.2. Gabapentin – Dysphagia

Authorisation procedure	Non-centralised
EPITT No	19296
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	17 January 2019

Recommendation

Having considered all the available evidence from literature, clinical trials and case reports from the post-marketing setting, the PRAC has agreed that dysphagia should be added as an adverse drug reaction to the product information of all gabapentin containing medicinal products. The MAHs of medicinal products containing gabapentin should submit a variation within 3 months[5] to amend the product information as described below (new text underlined). Based on the data from the clinical trial program, dysphagia should be added with the frequency uncommon:

Summary of product characteristics

4.8. Undesirable effects

Gastrointestinal disorders
Uncommon: dysphagia

Package leaflet

4. Possible side effects

Uncommon: may affect up to 1 in 100 people

- Difficulty swallowing

[5] Timeline added on 12 February 2019.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Acetylsalicylic acid	Evaluation of data on cancer-related mortality from a single study in elderly adults (19317)	Julia Pallos (HU)	Assess in the next PSUR (submission by 2 May 2019)	Bayer
Apixaban	Pancreatitis (19265)	Menno van der Elst (NL)	Supplementary information requested (submission by 8 February 2019)	Bristol-Myers Squibb / Pfizer EEIG
Atezolizumab	Anaphylactic reaction (19335)	Marcia Silva (PT)	Assess in the ongoing PSUR procedure (submission of the cumulative review by 15 March 2019)	Roche Registration GmbH
Dabigatran	Alopecia (19337)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 27 May 2019)	Boehringer Ingelheim International GmbH
Dimethyl fumarate	Arthritis and arthralgia (19338)	Martin Huber (DE)	Assess in the next PSUR (submission by 24 June 2019 for Tecfidera, by 3 March 2019 for Skilarence, by 26 August 2019 for Fumaderm)	Biogen Netherlands B.V., Almirall S.A
Dipeptidyl peptidase-4 (DPP-4) inhibitors[6]; glucagon-like peptide-1 (GLP-1) receptor agonists[7]	Increased risk of cholangiocarcinoma in adults with type 2 diabetes (19343)	Menno van der Elst (NL)	Supplementary information requested (submission by 6 March 2019)	Takeda Pharma A/S, Boehringer Ingelheim International GmbH, AstraZeneca AB, Merck Sharp & Dohme B.V., Novo Nordisk A/S, Novartis Europharm Limited, Sanofi-aventis groupe,

[6] Alogliptin; linagliptin; saxagliptin; sitagliptin; vildagliptin
[7] Albiglutide; dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
				GlaxoSmithKline Trading Services Limited, Eli Lilly Nederland B.V.
Pantroprazole	Colitis microscopic (19342)	Patrick Batty (UK)	Supplementary information requested (submission by 6 March 2019)	Takeda GmbH
Pregabalin	Respiratory depression with and without concomitant opioid use (19339)	Liana Gross-Martirosyan (NL)	Assess in the next PSUR (submission by 11 April 2019)	Pfizer Europe MA EEIG
Sertraline	Maculopathy (19341)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 6 March 2019)	Pfizer Limited
Temozolomide	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19332)	Martin Huber (DE)	Supplementary information requested (submission by 11 April 2019)	Merck Sharp & Dohme B.V.
Topiramate	Uveitis (19345)	Ulla Wändel-Liminga (SE)	Supplementary information requested (submission by 6 March 2019)	Janssen-Cilag

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Biotin	Interference with clinical laboratory tests (19156)	Martin Huber (DE)	· See section 1.1 · Follow up cases of ADR reports on biotin interference with laboratory tests as part of routine pharmacovigilance activities · Provide information in future PSURs	MAHs of biotin-containing medicinal products for oral use containing ≥ 150 microgram biotin per dose unit and medicinal products for parenteral use containing ≥60 microgram biotin per dose unit
Dolutegravir; abacavir sulfate, dolutegravir sodium, lamivudine; dolutegravir, rilpivirine	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women (19244)	Julie Williams (UK)	No further action for MAH	Viiv Healthcare
Nivolumab	Scleroderma (19282)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Bristol-Myers Squibb Pharma EEIG