8 July 2019[1]
EMA/PRAC/303951/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

# PRAC recommendations on signals

## Adopted at the 11-14 June 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 11-14 June 2019 (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 (24-27 June 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.

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] Intended 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.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Loperamide – Brugada syndrome in the context of abuse with loperamide*

| | |
|---|---|
| **Authorisation procedure** | Non-centralised |
| **EPITT No** | 19379 |
| **PRAC rapporteur(s)** | Adam Przybylkowski (PL) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Based on the review of the data on the risk of unmasking Brugada syndrome with loperamide, the PRAC has agreed that the MAH(s) of loperamide-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.4. Special warnings and precautions for use

Cardiac events including QT interval and QRS complex prolongation, torsade de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

4.9. Overdose

In individuals who have ingested overdoses of loperamide HCI, cardiac events such as QT interval and QRS complex prolongation, torsade de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

**Package leaflet**

No changes are needed.

[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. Propylthiouracil – Risk of congenital anomalies*

| | |
|---|---|
| **Authorisation procedure** | Non-centralised |
| **EPITT No** | 19358 |
| **PRAC rapporteur(s)** | Martin Huber (DE) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Having considered the available evidence in EudraVigilance and in the animal and epidemiological studies, the PRAC has agreed that the MAH(s) of propylthiouracil-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be informed about the potential risks of propylthiouracil use during pregnancy.

Pregnancy

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Propylthiouracil is able to cross the human placenta.

Animal studies are insufficient with respect to reproductive toxicity. Epidemiological studies provide conflicting results regarding the risk of congenital malformations.

Individual benefit/risk assessment is necessary before treatment with propylthiouracil during pregnancy. Propylthiouracil should be administered during pregnancy at the lowest effective dose without additional administration of thyroid hormones. If propylthiouracil is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

**Package leaflet**

2. What you need to know before you take [Product name]

Pregnancy

The potential of [Product name] to cause harm to an unborn baby is uncertain.

If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. You may need treatment with [Product name] during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby.

## *1.3. Rivaroxaban – Premature ending of the GALILEO study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19294 |
| **PRAC rapporteur(s)** | Ulla Wändel Liminga (SE) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Having considered the final results of the early terminated GALILEO study, available evidence in clinical trials and spontaneous reporting the PRAC has agreed that the MAH(s) of rivaroxaban-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.4.Special warnings and precautions for use

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of [Product name] have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that [Product name] provides adequate anticoagulation in this patient population. Treatment with [Product name] is not recommended for these patients.

**Package leaflet**

No changes are needed.

## *1.4. Secukinumab – Dermatitis exfoliative generalised*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19354 |
| **PRAC rapporteur(s)** | Eva Segovia (ES) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Having considered the available evidence from EudraVigilance, the literature and the cumulative review provided by Novartis, the PRAC has agreed that the MAH of Cosentyx (secukinumab) should submit a variation within 2 months to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.8. Undesirable effects

Skin and subcutaneous disorders

Rare: Exfoliative dermatitis [2)]

[2)] Cases were reported in patients with psoriasis diagnosis

**Package leaflet**

4. Possible side effects

Rare (may affect up to 1 in 1,000 people):

- severe allergic reaction with shock (anaphylactic reaction)
- redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis)

## *1.5. Sulfasalazine – Interference with dihydronicotinamide-adenine dinucleotide / dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays*

| | |
|---|---|
| **Authorisation procedure** | Non-centralised |
| **EPITT No** | 19351 |
| **PRAC rapporteur(s)** | Anette Kirstine Stark (DK) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered that the most recent data demonstrates that sulfasalazine poses a risk of interference with NAD(H)/NADP(H) based assays. Therefore, the PRAC has agreed that the MAHs for the sulfasalazine-containing products are to submit a variation within 2 months, to amend the product information as described below (new text underlined, text to be removed ~~struck-through~~):

**Summary of product characteristics**

4.4. Special warnings and precautions for use

[...]

Complete blood counts, including differential white cell count, and liver function tests, should be performed before starting sulfasalazine and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months, and as clinically indicated. Assessment of renal function (including urinalysis) should be performed in all patients initially and at least monthly for the first three months of treatment. Thereafter, monitoring should be performed as clinically indicated. The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice during sulfasalazine treatment may indicate myelosuppression, hemolysis, or hepatotoxicity. Discontinue treatment with sulfasalazine while awaiting the results of blood tests. **Please see Section 4.4 "Interference with laboratory testing".**

[...]

Interference with laboratory testing

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α-HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings

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

[…]

~~Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.~~

**Package leaflet**

2. What you need to know before you take sulfasalazine

Tell your doctor if you are taking or have recently taken [Product name], or any other sulfasalazine containing products, because they may affect results of blood and urine tests.

## *1.6. Temozolomide – Drug reaction with eosinophilia and systemic symptoms (DRESS)*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19332 |
| **PRAC rapporteur(s)** | Martin Huber (DE) |
| **Date of adoption** | 14 June 2019 |

## Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance and in the literature, and the known association of temozolomide with severe skin reactions, the PRAC has agreed that the MAH(s) of temozolomide-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.8. Undesirable effects

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders

Frequency 'not known': Drug reaction with eosinophilia and systemic symptoms (DRESS)

## *1.7. Topiramate – Uveitis*

| | |
|---|---|
| **Authorisation procedure** | Non-centralised |
| **EPITT No** | 19345 |
| **PRAC rapporteur(s)** | Ulla Wändel Liminga (SE) |
| **Date of adoption** | 14 June 2019 |

## Recommendation

Having considered the available evidence (including the MAH's cumulative review), reporting bilateral uveitis developing shortly after initiation of topiramate treatment in a few patients with no confounding disease and relatively rapid resolution of uveitis after cessation of topiramate treatment, the PRAC concluded that there is a causal association between topiramate and uveitis events. Therefore, the PRAC has agreed that the MAHs for the topiramate-containing products are to submit a variation within 2 months, to amend the product information as described below (new text underlined):

**Summary of product characteristics**

4.8. Undesirable effects

Eye disorders

Frequency not known: uveitis

**Package leaflet**

4. Possible side effects

Tell your doctor, or seek medical attention immediately if you have the following side effects:

Frequency not known (cannot be estimated from the available data):

- Inflammation of the eye (uveitis) with symptoms such as eye redness, pain, sensitivity to light, runny eyes, seeing small dots or getting blurred vision

## 2. Recommendations for submission of supplementary information

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Azacitidine | Progressive multifocal leukoencephalopathy (PML) (19422) | Menno van der Elst (NL) | Supplementary information requested (submission by 28 August 2019) | Celgene Europe BV |
| Durvalumab | Pemphigoid (19416) | David Olsen (NO) | Assess in the next PSUR (submission by 9 July 2019) | AstraZeneca AB |
| Pembrolizumab | Gastrointestinal ulcer (19427) | Menno van der Elst (NL) | Assess in the next PSUR (submission by 12 November 2019) | Merck Sharp & Dohme B.V. |

## 3. Other recommendations

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Dipeptidyl peptidase-4 (DPP-4) inhibitors[4]; glucagon-like peptide-1 (GLP-1) receptor agonists[5] | Increased risk of cholangiocarcinoma in adults with type 2 diabetes (19343) | Menno van der Elst (NL) | Routine pharmacovigilance | 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, GlaxoSmithKline Trading Services Limited, Eli Lilly Nederland B.V. |
| Temozolomide | Drug reaction with eosinophilia and systemic symptoms (DRESS) (19332) | Martin Huber (DE) | · See section 1.6<br>· Discuss the need for any potential amendments in the special warnings and precautions for use section of the summary of product characteristics and section 2 of the package leaflet (submission by 10 October 2020 in the next PSUR procedure) | Merck Sharp & Dohme B.V. |

[4] Alogliptin; linagliptin; saxagliptin; sitagliptin; vildagliptin
[5] Albiglutide; dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide