



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 14-17 April 2020 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 April 2020 (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 (28-30 April 2020) 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.



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 information³

1.1. Andexanet alfa – Erroneous assay results for levels of anti-factor Xa activity

Authorisation procedure	Centralised
EPITT No	19493
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	17 April 2020

Recommendation [see also section 3]

Having considered the available evidence, following the assessment of the Eudravigilance, literature and data obtained from the Marketing Authorisation Holder (MAH) of Ondexxya (Portola Netherlands B.V.), the PRAC has agreed the following recommendation:

1. The product information for Ondexxya (andexanet alfa) should be updated to reflect the risk of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa. The MAH of Ondexxya 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

4.4. Special warnings and precautions for use

Limitations of use

Clinical efficacy is based upon reversal of anti-FXa-activity in healthy volunteers dosed with apixaban or rivaroxaban. Andexanet alfa is not suitable for pre-treatment of urgent surgery. Use for edoxaban- or enoxaparin-reversal is not recommended due to lack of data. Andexanet alfa will not reverse the effects of non-FXa inhibitors (see section 5.1).

~~Although determination of anti-FXa activity in emergency situations is increasingly recommended, no recommendation for adapted andexanet alfa dosage is available. Therefore, Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response (i.e., achievement of haemostasis), lack of efficacy (i.e., re-bleeding), and adverse events (i.e., thromboembolic events). Treatment monitoring of andexanet alfa should not be based on anti-FXa-activity. Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa as these assays result in erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.~~

Dosage recommendation is based upon data-modelling in healthy volunteers. Validation has not been successful, yet. Data from bleeding patients are limited. Preliminary data suggest higher risk of thrombosis for patients receiving the higher dose of andexanet, previous lower dose of the anti-FXa inhibitor, and patients on rivaroxaban.

In ANNEXA-4, intracranial haemorrhage (ICH) patients (GCS > 7 and haematoma volume < 60 mL) have been included. Treatment of patients with more severe ICH with andexanet alfa has not been studied.

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

5.1. Pharmacodynamic properties

[...]

Pharmacodynamic effects

The effects of andexanet alfa can be measured through pharmacodynamic markers, including ~~anti-FXa activity, and~~ free fraction of available FXa inhibitor as well as through restoration of thrombin generation.

~~Anti-FXa activity correlates poorly to clinical efficacy and safety, making it unsuitable for dosing guidance (see section 4.4 and 5.1). Commercial anti-FXa activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa. Due to the reversible binding of andexanet alfa to the FXa inhibitor, the high sample dilution currently used in these assays leads to dissociation of the inhibitor from andexanet alfa, resulting in detection of erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.~~

In prospective, randomized, placebo-controlled, dose-ranging studies in healthy subjects, the dose and dose regimen of andexanet alfa required to reverse anti-FXa activity and restore thrombin generation for FXa inhibitors (apixaban or rivaroxaban) were determined with modified assays that are not commercially available.

1.2. Ibuprofen; ketoprofen; and fixed-dose combinations – Serious exacerbation of infections

Authorisation procedure	Centralised and non-centralised
EPITT No	19415
PRAC rapporteur(s)	Anette Kirstine Stark (DK)
Date of adoption	17 April 2020

Recommendation [see also section 3 for PedeA]

Based on the available data, the PRAC concluded that the risk of complications due to masking of symptoms of infection associated to the use of ibuprofen and ketoprofen containing products, cannot be excluded. Therefore, a product information update is deemed necessary.

Masking of signs and symptoms of an infection is a well-known risk of NSAIDs, and data from several studies indicates that the risk is clinically relevant mainly in the setting of bacterial community acquired pneumonia (CAP) and complications to varicella. Therefore, there is a need to update the current warnings on this risk.

The MAH(s) of ibuprofen and ketoprofen-containing medicinal product(s) should submit a variation within 6 months, to amend the product information of systemic products as described below (new text to be added underlined):

This text is to be adapted, at a national level, to the existing wordings in the product information of the ibuprofen and ketoprofen-containing medicinal product(s).

Summary of product characteristics

4.2. Posology and methods of administration

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

4.4. Special warnings and precautions for use

Masking of symptoms of underlying infections

[Product name] can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When [product name] is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Package leaflet

2. Warnings and precautions

Talk to your pharmacist or doctor if:

[...] you have an infection - please see heading "Infections" below.

[...]

Infections

[Product name] may hide signs of infections such as fever and pain. It is therefore possible that [product name] may delay appropriate treatment of infection, which may lead to an increased risk of complications. This has been observed in pneumonia caused by bacteria and bacterial skin infections related to chickenpox. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor without delay.

3. How to use [product name]

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. If you have an infection, consult a doctor without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

1.3. Idelalisib – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Centralised
EPITT No	19500
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	17 April 2020

Recommendation [see also section 3]

Based on the available data, the PRAC concluded that the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated to the use of idelalisib containing products cannot be excluded.

Therefore, the MAH(s) of idelalisib-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined, text to be removed ~~strike-through~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

Severe cutaneous reactions Stevens-Johnson syndrome and toxic epidermal necrolysis

~~Cases of Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) with fatal outcomes have been reported when have occurred with idelalisib. Cases of SJS and TEN with fatal outcomes have been reported when idelalisib was administered concomitantly with other medicinal products associated with these syndromes. If SJS, or TEN or DRESS is suspected, idelalisib should be immediately discontinued interrupted and the patient treated accordingly.~~

4.8. Undesirable effects

Table 2: Adverse drug reactions reported in clinical studies in subjects with haematologic malignancies receiving idelalisib and from post-marketing

Reaction	Any grade	Grade \geq 3
<i>Skin and subcutaneous tissue disorders</i>		
<u>Drug reaction with eosinophilia and systemic symptoms (DRESS)****</u>	<u>Not known</u>	<u>Not applicable</u>

**** observed in post-marketing data

Severe cutaneous reactions Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4)

~~Rarely, e~~ Cases of SJS, and TEN and DRESS have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, ~~and~~ amoxicillin, and sulfamethoxazole/trimethoprim). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted.

Package leaflet

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

Warnings and precautions

~~...Severe skin blistering conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with idelalisib treatment some people who have received Zydelig while also receiving other medicines known to cause these potentially life threatening conditions. Stop using idelalisib and seek medical attention immediately if you notice any of the symptoms described in section 4. Blistering can also involve the lining of the mouth genitals, and/or. Peeling away of the skin may lead to serious infection.~~

Tell your doctor right away:

- if you have redness and blistering of the skin
- if you have swelling and blistering of the lining of the mouth, throat, nose, genitals, and/or eyes

4. Possible side effects

STOP taking Zydelig and seek medical help immediately if you experience any of the following:

- reddish patches on the trunk, small circumscribed changes in the colour of the skin, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).
- ~~redness and blistering of the skin~~
- ~~swelling and blistering of the lining of the mouth, genitals, and/or eyes~~

1.4. Insulin⁴ – Cutaneous amyloidosis

Authorisation procedure	Centralised and non-centralised
EPITT No	19499
PRAC rapporteur(s)	Hans Christian Siersted (DK)
Date of adoption	17 April 2020

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of cutaneous amyloidosis with insulins, the PRAC has agreed that the MAHs of insulin-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, text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.2. Posology and method of administration

Method of administration

[...]

[Product name] is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

4.4. Special warnings and precautions for use

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

⁴ All insulin-containing products are concerned.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'not known': Cutaneous amyloidosis

Description of selected adverse reactions

~~Lipodystrophy~~ Skin and subcutaneous tissue disorders:

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (See section 4.4).

Package leaflet

2. What you need to know before you use [product name]

Skin changes at the injection site:

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use [product name]). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

4. Possible side effects

Skin changes at the injection site:

If you inject insulin too often at the same place, the fatty tissue may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

If the risk of lipodystrophy in section 4 of the package leaflet is listed under a frequency that is different from the above frequency for cutaneous amyloidosis the following update is proposed:

4. Possible side effects

[...]

~~Other side effects include:~~

[...]

~~Uncommon (may affect up to 1 in 100 people)~~

~~Changes under the skin where you use the injection (lipodystrophy):~~

Skin changes at the injection site:

If you inject insulin too often at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

Other side effects include:

[...]

Uncommon (may affect up to 1 in 100 people)

[...]

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
5 alfa-reductase inhibitors (5ARIs): finasteride; dutasteride	Type 2 diabetes mellitus (19424)	Annika Folin (SE)	Updated cumulative reviews of literature and clinical studies to be provided in next PSURs (submission by 17 February 2023 for dutasteride; check update of EURD list for finasteride next PSUR submission date)	MAHs of finasteride and dutasteride containing products with PSURs obligations
Abiraterone	Anaphylactic reaction (19535)	Eva A. Segovia (ES)	Supplementary information requested (submission by 2 July 2020)	Janssen-Cilag International NV
Bisoprolol	Angioedema (19542)	Kirsti Villikka (FI)	Supplementary information requested (submission by 2 July 2020)	Merck Serono Ltd
Ceftriaxone	Encephalopathy (19492)	Zane Neikena (LV)	Supplementary information requested (submission by 2 July 2020)	Roche
Paclitaxel	Progressive multifocal leukoencephalopathy (PML) (19553)	Menno van der Elst (NL)	Supplementary information requested (submission by 2 July 2020)	All MAHs with products containing paclitaxel authorised in the EEA and with at least one case concerning PML with paclitaxel as suspect drug in their pharmacovigilance databases

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pomalidomide	Progressive multifocal leukoencephalopathy (PML) (19546)	Eva A. Segovia (ES)	Supplementary information requested (submission by 2 July 2020)	Celgene Europe BV
Tumour necrosis factor alpha inhibitors: adalimumab; certolizumab pegol; etanercept; golimumab; infliximab	Kaposi's sarcoma (19480)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 8 May 2020)	AbbVie Deutschland GmbH & Co., UCB Pharma S.A., Pfizer Europe MA EEIG, Janssen Biologics B.V.
Vedolizumab	Evans' syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura (19547)	Adam Przybylowski (PL)	Supplementary information requested (submission by 2 July 2020)	Takeda Pharma A/S

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Autoimmune encephalitis (19483)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	MAHs of adalimumab containing products
Andexanet alfa	Erroneous assay results for levels of anti-factor Xa activity (19493)	Menno van der Elst (NL)	<ul style="list-style-type: none"> · See section 1.1 · Monitor in upcoming PSURs · Include key elements defined by PRAC in the Direct Healthcare Professional Communication (DHPC) to be finalised and distributed as per the time schedule agreed within the type II variation EMEA/H/C/004108/II/0011 	Portola Netherlands B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ibuprofen	Serious exacerbation of infections (19415)	Anette Kirstine Stark (DK)	Routine pharmacovigilance	Recordati Rare Diseases (MAH of Pedeia)
Idelalisib	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19500)	Martin Huber (DE)	<ul style="list-style-type: none"> · See section 1.4 · Monitor serious cutaneous adverse reactions in forthcoming PSURs 	MAHs of idelalisib-containing medicinal products