



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

11 May 2020<sup>1</sup>  
EMA/PRAC/201788/2020  
Pharmacovigilance Risk Assessment Committee (PRAC)

## New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 14-17 April 2020 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found [here](#) (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

### 1. Andexanet alfa – Erroneous assay results for levels of anti-factor Xa activity (EPITT no 19493)

#### Summary of product characteristics

##### 4.4. Special warnings and precautions for use

Limitations of use

[...]

~~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.~~

[...]

---

<sup>1</sup> Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).



### 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.

## **2. Ibuprofen, ketoprofen and fixed-dose combinations for systemic use – Serious exacerbation of infections (EPITT no 19415)**

### **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).

## **3. Idelalisib – Drug reaction with eosinophilia and systemic symptoms (DRESS) (EPITT no 19500)**

### **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). [...]~~

## 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 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~~

## 4. Insulin<sup>2</sup> – Cutaneous amyloidosis (EPITT no 19499)

### 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

---

<sup>2</sup> All insulin-containing products are concerned.

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.

#### 4.8. 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)

[...]