5 February 2024[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 8-11 January 2024 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 on the webpage for PRAC recommendations on safety signals (in English only).

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

1. Amphotericin B, lipid formulations – Hyperkalaemia (EPITT no 19966)

AmBisome*

Summary of product characteristics

4.4 Special warnings and precautions for use

AmBisome has been shown to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity; however, adverse reactions, including renal adverse reactions, may still occur.

In studies comparing AmBisome 3mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was found that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia were notably higher in the high dose groups.

Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium, as well as renal, hepatic and haematopoietic function should be performed ~~in patients receiving concomitant nephrotoxic medications as well as other patients treated with AmBisome (see section 4.5)~~. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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AmBisome administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalaemia. Therefore, renal function and laboratory evaluation of potassium, should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications (see section 4.5).

4.8 Undesirable effects

Under SOC Metabolism and nutrition disorders with frequency "Common"

Hyperkalaemia

Package leaflet

2. What you need to know before you use AmBisome

Warning and precautions

- **If you are taking other medicines that may cause kidney damage**, see the section *Other medicines and AmBisome*. AmBisome may cause damage to the kidney. Your doctor or nurse will take ~~regular~~ blood samples to measure your creatinine (a chemical in the blood that reflects kidney function), and electrolyte levels (particularly potassium and magnesium) before and during the treatment with AmBisome because both of these can be abnormal if you have changes in your kidney function. This is particularly important if you have previous renal damage or if you are taking other medicines that can affect the way your kidney functions. The blood samples will also be tested for changes in your liver, and your body's ability to produce new blood cells and platelets. **If blood tests show a change in kidney function**, or other important changes your doctor may give you a lower dose of AmBisome or stop treatment.
- **If blood tests show that your potassium levels are low.** If this happens, your doctor may prescribe a potassium supplement for you to take while you are treated with AmBisome.
- **If blood test shows that your potassium levels are high** you may suffer irregular heartbeat, sometimes severe.

4. Possible side effects

- Common side effects (may affect up to 1 in 10 people treated)
- ……
- High blood potassium levels

Abelcet*

Summary of product characteristics

4.4 Special warnings and precautions for use

Since Abelcet is a potentially nephrotoxic drug, monitoring of renal function should be performed before initiating treatment and during the treatment. This is particularly important in patients with pre-existing renal disease, ~~or~~ who have already experienced renal failure, or in patients receiving nephrotoxic medications. Laboratory evaluation of serum electrolytes, particularly potassium ~~as well as renal function~~ should be performed regularly before and during therapy. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Some of them occurred in patients with renal impairment, or after potassium supplementation in patients with previous hypokalaemia.

4.8 Undesirable effects

Under SOC Metabolism and nutrition disorders with frequency "Common"

Hyperkalaemia*

Package leaflet

2. What you need to know before you use Abelcet

Warning and precautions

If you are treated with Abelcet lipid complex, your doctor will monitor the function of the kidneys and the electrolytes such as potassium prior and during treatment with Abelcet. This is particularly important if you have previous kidney damage or if you are taking other medicines that can affect the way your kidney functions. If blood test show that your potassium levels are high you may suffer irregular heartbeat, sometimes severe.

Your doctor will regularly monitor the function of your ~~kidneys and~~ liver ~~and have regular blood tests~~, especially if you have had liver disease in the past ~~have had kidney problems~~.

4. Possible side effects

Common side effects

……

High blood potassium levels*

** Due to differences in the national summaries of product characteristics and Package Leaflets, it is acknowledged that text already included in the product information will have to be modified/adjusted in order to accommodate the new text stated in this PRAC recommendation.*

2. Avatrombopag – Antiphospholipid syndrome (EPITT no 19954)

Summary of product characteristics

4.4 Special warnings and precautions for use

Thrombotic/thromboembolic events

[…] Doptelet was not studied in patients with prior thromboembolic events. Consider the potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (e.g. Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency), acquired risk factors (e.g. antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, […]

3. Cefotaxime – Drug reaction with eosinophilia and systemic symptoms (DRESS) (EPITT no 19960)

Summary of product characteristics

4.4 Special warnings and precautions for use

The current text should be replaced with the following:

Severe skin reactions

Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime treatment.

At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

If signs and symptoms suggestive of these reactions appear, cefotaxime should be withdrawn immediately. If the patient has developed AGEP, SJS, TEN or DRESS with the use of cefotaxime, treatment with cefotaxime must not be restarted and should be permanently discontinued.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to cefotaxime in children that develop symptoms of rash and fever during therapy with cefotaxime.

4.8 Undesirable effects

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known"

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Package leaflet

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

Do not take [product name] if:

……

You have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking cefotaxime or other cephalosporins.

Do not have this [product name] or tell your doctor if any of these apply to you.

Warning and precautions

Take special care with [product name]

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with cefotaxime treatment. Stop using cefotaxime and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

The current text should be replaced with the following:

Stop taking cefotaxime and tell your doctor immediately if you notice any of the following symptoms:

- Reddish non-elevated, target-like or circular patches on the trunk, 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).
- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).

4. Cobimetinib; vemurafenib – Aphthous ulcer, mouth ulceration, stomatitis (EPITT no 19961)

- **Zelboraf (vemurafenib)**

Summary of product characteristics

4.8 Undesirable effects

Gastrointestinal disorders

Frequency 'common': Stomatitis

Package leaflet

4. Possible side effects

Common (may affect up to 1 in 10 people):

<…>

- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)

- **Cotellic (cobimetinib)**

Summary of product characteristics

4.8 Undesirable effects

Gastrointestinal disorders

Frequency 'very common': Stomatitis

Package leaflet

4. Possible side effects

Very common (may affect more than 1 in 10 people):

<…>

- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)