11 June 2018[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 14-17 May 2018 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. Apixaban; edoxaban – Drug interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors (SSRI) and/or serotonin and noradrenaline reuptake inhibitors (SNRI) leading to increased risk of bleeding (EPITT no 19139)

Edoxaban

Summary of product characteristics

4.4. Special warnings and precautions for use

~~*Anticoagulants, antiplatelets, and thrombolytics*~~ *Interaction with other medicinal products affecting haemostasis*

Concomitant use of medicines affecting haemostasis may increase the risk of bleeding. These include acetylsalicylic acid (ASA), P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and chronic nonsteroidal anti-inflammatory drugs (NSAIDs) (see section 4.5).

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

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

Anticoagulants, antiplatelets, ~~and~~ NSAIDs and SSRIs/SNRIs

[…]

SSRIs/SNRIs: As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets (see section 4.4).

Package leaflet

2. What you need to know before you take Lixiana/Roteas

Other medicines and Lixiana/Roteas

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are taking any of the following:

- […]
- anti-inflammatory and pain-relieving medicines (e.g. naproxen or acetylsalicylic acid (aspirin))
- antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors

Apixaban

Summary of product characteristics

4.4. Special warnings and precautions for use

Interaction with other medicinal products affecting haemostasis

[…]

Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

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

Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs

[…]

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are coadministered with apixaban. Eliquis should be used with caution when coadministered with SSRIs/SNRIs or NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).

Package leaflet

2. What you need to know before you take Eliquis

Other medicines and Eliquis

[…]

The following medicines may increase the effects of Eliquis and increase the chance for unwanted bleeding:

- […]
- **medicines for high blood pressure or heart problems** (e.g., diltiazem)
- **antidepressant medicines** called **selective serotonin re-uptake inhibitors** or **serotonin-norepinephrine re-uptake inhibitors**

2. Lenalidomide – Progressive multifocal leukoencephalopathy (PML) (EPITT no 19130)

Summary of product characteristics

4.4. Special warnings and precautions for use

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

Package leaflet

2. What you need to know before you use REVLIMID […]

Warnings and precautions

At any time during or after your treatment, tell your doctor or nurse immediately if you: experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). If you had these symptoms prior to treatment with lenalidomide, tell your doctor about any change in these symptoms.

3. Lenograstim; lipegfilgrastim; pegfilgrastim – Pulmonary haemorrhage (EPITT no 19181)

Summary of product characteristics

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Haemoptysis (uncommon*)

Pulmonary haemorrhage (rare*)

Package leaflet

4. Possible side effects

(under corresponding frequencies):

Coughing up blood (haemoptysis) – uncommon*

Bleeding from the lung (pulmonary haemorrhage) – rare*

*Note: Stated frequencies are applicable for pegfilgrastim; for lipegfilgrastim and lenograstim the frequency is to be calculated by the MAHs.

4. Pembrolizumab – Aseptic meningitis (EPITT no 19115)

Summary of product characteristics

4.8. Undesirable effects

Nervous system disorders

Frequency 'rare': meningitis (aseptic)

Package Leaflet

4. Possible side effects

Rare (may affect up to 1 in 1,000 people)
Inflammation of the membrane around the spinal cord and brain, which may present as neck stiffness, headache, fever, eye sensitivity to light, nausea and vomiting (meningitis)