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EMA/PRAC/287231/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 14-17 May 2018 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 May 2018 (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 (28-31 May 2018) 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.

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. 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

Authorisation procedure	Centralised
EPITT No	19139
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	17 May 2018

Recommendation

The PRAC has considered the available evidence from EudraVigilance and the literature, including the response from Bristol-Myers Squibb and Daiichi Sankyo Europe GmbH, as well as the biological plausibility of an interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) resulting in an increased risk of bleeding. In the light of this evidence, the PRAC has agreed that the MAH(s) of apixaban and edoxaban containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined, text to be removed ~~struck through~~):

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).

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

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

[To be added as last paragraph before “Effect of edoxaban on other medicines”]

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).

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

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:

- some medicines for fungal infections (e.g. ketoconazole)
- medicines to treat abnormal heart beat (e.g. dronedarone, quinidine, verapamil)
- other medicines to reduce blood clotting (e.g. heparin, clopidogrel or vitamin K antagonists such as warfarin, acenocoumarol, phenprocoumon or dabigatran, rivaroxaban, apixaban)
- antibiotic medicines (e.g. erythromycin)
- medicines to prevent organ rejection after transplantation (e.g. ciclosporin)
- 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

Tell your doctor before taking Lixiana/Roteas, because these medicines may increase the effects of Lixiana/Roteas and the chance of unwanted bleeding. Your doctor will decide, if you should be treated with Lixiana/Roteas and if you should be kept under observation.

Apixaban

Summary of product characteristics

4.4. Special warnings and precautions for use

Interaction with other medicinal products affecting haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding (see section 4.5).

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

[To stay before paragraph starting with “Medicinal products associated with serious bleeding”]

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

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

Some medicines may increase the effects of Eliquis and some may decrease its effects. Your doctor will decide, if you should be treated with Eliquis when taking these medicines and how closely you should be monitored.

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

- some **medicines for fungal infections** (e.g., ketoconazole, etc.)
- some **antiviral medicines for HIV / AIDS** (e.g., ritonavir)
- other **medicines that are used to reduce blood clotting** (e.g., enoxaparin, etc.)
- **anti-inflammatory or pain medicines** (e.g., acetylsalicylic acid or naproxen). Especially, if you are older than 75 years and are taking acetylsalicylic acid, you may have an increased chance of 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**

1.2. Lenalidomide – Progressive multifocal leukoencephalopathy (PML)

Authorisation procedure	Centralised
EPITT No	19130
PRAC rapporteur(s)	Ghania Chamouni (FR)
Date of adoption	17 May 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of progressive multifocal leukoencephalopathy (PML), the PRAC has agreed that the MAH of lenalidomide (Revlimid) 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

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.

1.3. Lenograstim; lipegfilgrastim; pegfilgrastim – Pulmonary haemorrhage

Authorisation procedure	Centralised and non-centralised
EPITT No	19181
PRAC rapporteur(s)	Patrick Batty (UK)
Date of adoption	17 May 2018

Recommendation

Having considered the evidence from the EudraVigilance database, the possibility of a class effect and the responses from MAHs, the PRAC recommended that the MAHs¹ of pegfilgrastim, lenograstim² and lipegfilgrastim should submit a variation within 60 days to update the product information as described below (new text underlined):

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.

¹Applicants for products under evaluation should update their product information accordingly during evaluation.

²To include pulmonary haemorrhage and haemoptysis for both cancer patients and healthy donors.

1.4. Pembrolizumab – Aseptic meningitis

Authorisation procedure	Centralised
EPITT No	19115
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	17 May 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH for Keytruda (Merck Sharp & Dohme Limited) 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

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)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban	Neutropenia (19187)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 26 July 2018)	Bristol-Myers Squibb / Pfizer EEIG
Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: daclatasvir; dasabuvir; elbasvir, grazoprevir; glecaprevir; pibrentasvir; ledipasvir, sofosbuvir; ombitasvir, paritaprevir, ritonavir; sofosbuvir; sofosbuvir, velpatasvir; sofosbuvir, velpatasvir, voxilaprevir	Dysglycaemia (19234)	Julie Williams (UK)	Supplementary information requested (submission by 4 July 2018)	AbbVie Ltd, Bristol-Myers Squibb Pharma EEIG, Gilead Sciences International Ltd, Merck Sharp & Dohme Limited
Dolutegravir	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women (19244)	Julie Williams (UK)	Supplementary information requested (submission by 25 May 2018); direct healthcare professional communication (DHPC) requested	ViiV Healthcare B.V.
Dulaglutide	Acute kidney injury (19204)	Carmela Macchiarulo (IT)	Supplementary information requested (submission by 20 July 2018)	Eli Lilly Nederland B.V.
Hormonal contraceptives	Suicidality with hormonal contraceptives following a recent publication (19144)	Doris Stenver (DK)	Supplementary information requested (submission by 1 August 2018)	Innovator MAHs for hormonal contraceptives

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Hydroxycarbamide	Progressive multifocal leukoencephalopathy (PML) (19210)	Laurence de Fays (BE)	Assess in the PSURs (submission within 30 days in the ongoing PSUSA procedure for MAHs involved in the PSUSA/00009182/2017 12; submission in the next PSUR by 6 September 2018 for Addmedica)	MAHs of hydroxycarbamide-containing products
Ipilimumab	Cytomegalovirus gastrointestinal infection (19207)	Sabine Straus (NL)	Supplementary information requested (submission by 4 July 2018)	Bristol-Myers Squibb Pharma EEIG
Meningococcal group b vaccine (rDNA, component, adsorbed)	Meningism (19224)	Qun-Ying Yue (SE)	Assess within the ongoing PSUSA/00010043/2018 01 procedure (submission by 15 June 2018)	GSK Vaccines S.r.l
Niraparib	Potential occurrence of embolic and thrombotic events (19206)	Patrick Batty (UK)	Assess in the next PSUR (submission by 4 June 2018)	Tesaro UK Limited
Nivolumab	Cholangitis sclerosing (19203)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 11 September 2018)	Bristol-Myers Squibb Pharma EEIG
Oxybutynin; carbamazepine	Drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations	Laurence de Fays (BE)	Supplementary information requested (submission by 1 August 2018)	MAHs of oxybutynin containing medicinal products (Teva BV/Nicobrand Ltd, Accord Healthcare Ltd., Arafarma Group, Aurobindo Pharma BV, Mylan, Sanofi, Tillomed Laboratories Ltd., Takeda, Janssen-Cilag); MAH innovator of carbamazepine (Novartis)

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Teriflunomide	Dyslipidaemia (19227)	Martin Huber (DE)	Supplementary information requested (submission by 4 July 2018)	Sanofi-aventis Groupe
Tocilizumab	Noninfectious encephalitis (19197)	Brigitte Keller-Stanislawski (DE)	Assess in the ongoing PSUR (submission with the comments to the ongoing PSUR assessment report)	Roche Registration GmbH
Trastuzumab; trastuzumab emtansine; pertuzumab	Multiple sclerosis relapse (19208)	Doris Stenver (DK)	Supplementary information requested (submission by 1 August 2018)	Roche Registration GmbH; Celltrion Healthcare Hungary Kft.; Samsung Bioepis UK Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban	Tubulointerstitial nephritis (19127)	Menno van der Elst (NL)	Routine pharmacovigilance	Bristol-Myers Squibb / Pfizer EEIG