6 May 2019[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 April 2019 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 8-11 April 2019 (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 (23-26 April 2019) 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.

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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 information[3]

1.1. Direct-acting oral anticoagulants (DOACs): apixaban; dabigatran etexilate; edoxaban; rivaroxaban – Recurrent thrombosis in patients with antiphospholipid syndrome

Authorisation procedure	Centralised
EPITT No	19320
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	11 April 2019

Recommendation *[see also section 3]*

Having considered all the available evidence from literature, clinical trials and case reports from the post-marketing setting, the PRAC has agreed that the MAHs of rivaroxaban, apixaban, edoxaban and dabigatran etexilate (Direct acting Oral Anticoagulants (DOACs)) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

Rivaroxaban/apixaban/edoxaban/dabigatran etexilate

4.4. Special warnings and precautions for use

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban/apixaban/edoxaban/dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Rivaroxaban

5.1. Pharmacodynamic properties

Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) <50 mL/min) and 61 to warfarin (INR 2.0- 3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomized to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

[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

Rivaroxaban/dabigatran etexilate

2. What you need to know before you take Xarelto/Pradaxa

Take special care with Xarelto/Pradaxa

- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

Apixaban/edoxaban

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

Warnings and precautions

Take special care with Eliquis/Lixiana/Roteas

If you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

1.2. Modafinil – Evaluation of data on foetal outcomes including congenital anomalies from a single observational study in the US

Authorisation procedure	Non-centralised
EPITT No	19367
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	11 April 2019

Recommendation *[see also section 3]*

All MAHs of modafinil-containing medicinal products should submit a variation within 2 months of the publication date 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

4.6. Fertility, pregnancy and lactation

~~There is limited data on the use of modafinil in pregnant women.~~

Based on limited human experience from a pregnancy registry and spontaneous reporting modafinil is suspected to cause congenital malformations when administered during pregnancy.

Studies in animals have shown reproductive toxicity (see section 5.3).

~~Modafinil is not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception.~~

[Product name] should not be used during pregnancy.

Women of childbearing potential have to use effective contraception. As modafinil may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see sections 4.4 and 4.5).

Package leaflet

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

Pregnancy and breast-feeding

If you are pregnant (or think that you may be), are planning to become pregnant, or are breast feeding, you should not take [product name]. ~~It is not known if your medicine may harm your unborn baby.~~

Modafinil is suspected to cause birth defects if taken during pregnancy.

Talk to your doctor about the birth control methods that will be right for you while you are taking [product name] (and for two months after stopping) or if you have any other concerns.

1.3. Selective serotonin reuptake inhibitors: citalopram; escitalopram – Drug interaction with fluconazole

Authorisation procedure	Non-centralised
EPITT No	19327
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	11 April 2019

Recommendation

PRAC noted that the additional data provided by the MAH did not give further evidence for a drug-drug interaction between citalopram/escitalopram and fluconazole with a clinically relevant impact. Considering the huge exposure for citalopram/escitalopram only a few possible interaction cases were identified. Nevertheless, fluconazole is a potent inhibitor of CYP2C19 and a moderate inhibitor of CYP3A4. Both isozymes are involved in the metabolism of citalopram/escitalopram. Therefore, there is a mechanistic rationale for a PK interaction, which warrants an update of the product information. The PRAC has agreed that the MAH(s) of citalopram/escitalopram containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.5 Interaction with other medicinal products and other forms of interaction

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of [active substance] may be necessary based on monitoring of side-effects during concomitant treatment (see section 4.4).

Package leaflet

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

Other medicines and [Product name]

Cimetidine, lansoprazole and omeprazole (used to treat stomach ulcers), fluconazole (used to treat fungal infections), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). These may cause increased blood levels of [active substance].

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Benralizumab	Pneumonia (19368)	David Olsen (NO)	Assess in the next PSUR (submission by 22 July 2019)	AstraZeneca AB
Ibrutinib	Ischemic stroke (19369)	Nikica Mirošević Skvrce (HR)	Supplementary information requested (submission by 3 July 2019)	Janssen-Cilag International NV
Ivacaftor; ivacaftor, tezacaftor	Increased blood creatine phosphokinase (CPK) (19316)	Rhea Fitzgerald (IE)	Assess in the next PSUR (submission by 20 October 2019)	Vertex Pharmaceuticals (Europe) Ltd.
Omalizumab	Acquired haemophilia (19385)	Annika Folin (SE)	Supplementary information requested (submission by 11 June 2019)	Novartis Europharm Limited
Pembrolizumab	Optic neuritis (19381)	Menno van der Elst (NL)	Supplementary information requested (submission by 3 July 2019)	Merck Sharp & Dohme B.V.
Perampanel	Hepatotoxicity (19383)	Julie Williams (UK)	Supplementary information requested (submission by 3 July 2019)	Eisai GmbH
Teriflunomide	Psoriasis (19366)	Martin Huber (DE)	Supplementary information requested (submission by 3 July 2019)	Sanofi-aventis groupe
Ticagrelor	Severe cutaneous adverse reactions (SCARs) (19375)	Menno van der Elst (NL)	Supplementary information requested (submission by 3 July 2019)	AstraZeneca AB

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Direct-acting oral anticoagulants (DOACs): apixaban; dabigatran etexilate; edoxaban; rivaroxaban	Recurrent thrombosis in patients with antiphospholipid syndrome (19320)	Ulla Wändel Liminga (SE)	· See section 1.1 · Circulate a Direct Healthcare Professional Communication (DHPC)	Bayer AG, Bristol-Myers Squibb / Pfizer EEIG, Boehringer Ingelheim International GmbH, Daiichi Sankyo Europe GmbH
Idelalisib	Arthritis and arthralgia (19312)	Martin Huber (DE)	Routine pharmacovigilance	Gilead Sciences Ireland UC
Inactivated poliomyelitis vaccine, including combination vaccines	Case reports from outside the EU of immune thrombocytopenic purpura (19336)	Anette Kirstine Stark (DK)	Routine pharmacovigilance	MAHs of inactivated poliomyelitis vaccine, including combination vaccines
Loperamide	Brugada syndrome in the context of abuse with loperamide (19379)	Adam Przybyłkowski (PL)	Provide comments on the proposed updates to the product information (submission by 11 May 2019)	Johnson & Johnson Consumer B.V.
Modafinil	Evaluation of data on foetal outcomes including congenital anomalies from a single observational study in the US (19367)	Martin Huber (DE)	· See section 1.2 (all MAHs) · Submit a variation to update section 5.3 of the summary of product characteristics (Teva) · Align section 5.3 of the summary of product characteristics with the wording implemented by Teva (all MAHs) · Update the risk management plan (RMP) (MAHs with an RMP in place) · Submit a study	Teva (innovator MAH for modafinil); all other MAHs of modafinil-containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
			synopsis (Teva) · Revise the PSUR frequency to 1 year (all MAHs) · Provide interim reports from the NUVIGIL/PROVIGIL pregnancy registry in future PSURs (Teva) · Agree on communication at national level with national competent authorities (Teva)	
Sorafenib	Acute generalised exemanthous pustulosis (AGEP) (18109)	Annika Folin (SE)	Routine pharmacovigilance	Bayer AG