15 September 2016
EMA/PRAC/551805/2016 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 30 August-2 September 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 30 August-2 September 2016 (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 (12-15 September 2016) 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] Please see footnote on pages 5 and 6 regarding corticosteroids.
[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. Agomelatine – Urinary retention

Authorisation procedure	Centralised
EPITT No	18637
PRAC rapporteur(s)	Kristin Kvande (NO)
Date of adoption	2 September 2016

Recommendation

The MAH(s) of agomelatine-containing medicinal products 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

Renal and urinary disorders

Frequency "rare": Urinary retention

Package leaflet

4 - Possible side effects

Frequency "rare": Inability to completely empty the bladder

1.2. Boceprevir ; daclatasvir; dasabuvir; elbasvir, grazoprevir; ledipasvir, sofosbuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, velpatasvir – Drug interaction between direct-acting antivirals (DAAV) and vitamin K antagonists leading to a reduced international normalised ratio (INR)

Authorisation procedure	Centralised
EPITT No	18654
PRAC rapporteur(s)	Dolores Montero (ES)
Date of adoption	2 September 2016

Recommendation

Having considered the available evidence from case reports and the biological plausibility of changes in International Normalised Ratio (INR) in patients treated with direct-acting antivirals against hepatitis C and vitamin K antagonists due to changes in liver function, and also taken into consideration the comments submitted by AbbVie Ltd, Bristol-Myers Squibb, Gilead Sciences International Ltd, Janssen-Cilag and Merck Sharp & Dohme Limited, the PRAC has agreed that the MAHs of direct-acting antivirals

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

against hepatitis C (Daklinza, Exviera, Harvoni, Olysio, Sovaldi, Victrelis, Viekirax, Epclusa and Zepatier) 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

Patients treated with vitamin K antagonists:

As liver function may change during treatment with {product name}, a close monitoring of International Normalised Ratio (INR) values is recommended.

Moreover, the tables with information on interactions should be modified according to the following instructions:

For Olysio, Viekirax and Exviera (products for which pharmacokinetic studies with warfarin have been performed)

Warfarin and other vitamin K antagonists	Interaction	Recommendation/clinical comments
	Results of interaction studies with warfarin should be included here as applicable	While no change in the pharmacokinetics of warfarin is expected, close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with {product name}.

For Victrelis, Sovaldi, Harvoni, Daklinza, Zepatier and Epclusa (products for which pharmacokinetic studies with warfarin have not been performed)

Vitamin K antagonists	Interaction	Recommendation/ clinical comments
	Interaction not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with {product name}.

Package leaflet

2 - What you need to know before you <take> <use> {product name}

Other medicines and {product name}

<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.>

Warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

Note: it is acknowledged that the package leaflet for some products may need to be slightly modified in order to incorporate the above message.

1.3. Cobicistat containing products: cobicistat; cobicistat, atazanavir sulfate; cobicistat, darunavir; cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide; cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil fumarate – Drug interaction with corticosteroids leading to adrenal suppression[4]

Authorisation procedure	Centralised
EPITT No	18647
PRAC rapporteur(s)	Rafe Suvarna (UK)
Date of adoption	2 September 2016

Recommendation

The PRAC has reviewed the recommendations for risk minimisation provided by Bristol-Myers Squibb and Janssen-Cilag as well as the data provided by the MAH Gilead which indicated a low reporting rate for events of adrenal suppression/insufficiency and Cushing's syndrome occurring in relation to co-administration of corticosteroids with cobicistat containing products. The PRAC has agreed that while no warning regarding this in Section 4.4 of the summary of product characteristics (SmPC) is required at present, the wording in Section 4.5 of the SmPCs and package leaflets (PLs) should be strengthened to indicate that the cases of adrenal suppression and Cushing's syndrome have been identified in relation to the interaction. The MAHs of cobicistat containing medicinal products should therefore submit a variation within 2 months, to amend the product information as described below, so that the SmPC and PL wording is aligned for all cobicistat containing products (new wording underlined).

The MAHs of all corticosteroid medicines (excluding topical formulations) should also submit a variation within 3 months to update their SmPC and PL accordingly to reflect this interaction, as described below (new wording underlined).

SmPC of cobicistat containing products

N.B: For Evotaz, Section 4.4 warning should be maintained.

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

Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone,	Interaction not studied with any of the components of <product name>.	Concomitant use of <product name> and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other

[4] The amendments of the product information for corticosteroids have been further reviewed by PRAC at its 24-27 October 2016 meeting, hence the wording published in this document for corticosteroids no longer applies. The new product information wording for corticosteroids will be published at the end of November 2016.

mometasone, prednisone, triamcinolone).	Plasma concentrations of these medicinal products may be increased when co–administered with <product name>, resulting in reduced serum cortisol concentrations.	inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.

PL of cobicistat containing products

2 - What you need to know before you take {product name}

It is important to tell your doctor if you are taking:

Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.

SmPC of corticosteroids (excluding topical formulations)[5]

4.4. Special warnings and precautions for use *or* 4.5. Interaction with other medicinal products and other forms of interaction, *as appropriate*

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

[5] The amendments of the product information for corticosteroids have been further reviewed by PRAC at its 24-27 October 2016 meeting, hence the wording published in this document for corticosteroids no longer applies. The new product information wording for corticosteroids will be published at the end of November 2016.

1.4. Iomeprol – Haemolysis

Authorisation procedure	Non centralised
EPITT No	18625
PRAC rapporteur(s)	Helga Haugom Olsen (NO)
Date of adoption	2 September 2016

Recommendation

Having considered the available evidence in EudraVigilance and literature and the data submitted by the MAHs, the PRAC has agreed that the MAHs of iomeprol-containing medicinal products 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

Blood and lymphatic system disorders (frequency not known):

Haemolytic anaemia

Package leaflet

4 - Possible side effects

Frequency not known

Haemolytic anaemia (abnormal breakdown of red blood cells, which may cause fatigue, rapid heart rate and shortness of breath)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azacitidine	Pericarditis and pericardial effusion (18733)	Sabine Straus (NL)	Supplementary information requested (submission by 9 November 2016)	Celgene Europe Limited
Darbepoetin alfa	Incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions (18718)	Valerie Straßmann (DE)	Supplementary information requested (submission by 9 November 2016)	Amgen Europe B.V.
Lenalidomide	Hemophagocytic lymphohistiocytosis (HLH) (18689)	Claire Férard (FR)	Supplementary information requested (submission by 9 November 2016)	Celgene Europe Limited
Propofol; valproate	Pharmacokinetic drug interaction leading to an increased propofol exposure (18696)	Helga Haugom Olsen (NO)	Supplementary information requested (submission by 9 November 2016)	AstraZeneca
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole ; pantoprazole; rabeprazole	Incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD) (18698)	Rafe Suvarna (UK)	Supplementary information requested (submission by 9 November 2016)	Takeda; Janssen-Cilag; Eisai; AstraZeneca
Ritonavir	Retinal pigment epitheliopathy (18703)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 29 November 2016)	AbbVie Ltd.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Agomelatine	Leukopenia (18638)	Kristin Kvande (NO)	Monitor in PSUR	Servier
Esomeprazole	Gastric polyps (18725)	Qun-Ying Yue (SE)	No action at this stage	Not applicable
Selective serotonin reuptake inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; mirtazapine; paroxetine; sertraline; and Serotonin–noradrenaline reuptake inhibitors (SNRIs): duloxetine; sibutramine; venlafaxine	Risk of autism spectrum disorders (ASD) after maternal use of SSRI/SNRI (14082)	Claire Férard (FR)	Routine pharmacovigilance	MAHs of SSRIs and SNRIs