29 October 2018[1]
EMA/PRAC/689235/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 1-4 October 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 1-4 October 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 (17-20 October 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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 antivirals (DAAV) indicated for the treatment of hepatitis C[4] – Dysglycaemia

Authorisation procedure	Centralised
EPITT No	19234
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	4 October 2018

Recommendation *[see also section 3]*

Having considered the available evidence in the literature and EudraVigilance, and the responses from the MAHs, the PRAC has agreed that the MAHs for direct-acting antivirals against hepatitis C (Daklinza, Epclusa, Exviera, Harvoni, Maviret, Sovaldi, Viekirax, Vosevi, Zepatier) 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

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV {direct acting antiviral / DAA} treatment. Glucose levels of diabetic patients initiating {direct acting antiviral / DAA} therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when {direct acting antiviral / DAA} therapy is initiated.

Package leaflet

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

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine if you:

- Have diabetes. You may need closer monitoring of your blood glucose levels and/or adjustment of your diabetes medication after starting {product name}. Some diabetic patients have experienced low sugar levels in the blood (hypoglycaemia) after starting treatment with medicines like {product name}.

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.
[4] Daclatasvir; dasabuvir; elbasvir, grazoprevir; glecaprevir, pibrentasvir; ledipasvir, sofosbuvir; ombitasvir, pariteprevir, ritonavir; sofosbuvir; sofosbuvir, velpatasvir; sofosbuvir, velpatasvir, voxilaprevir

1.2. Dolutegravir – Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women

Authorisation procedure	Centralised
EPITT No	19244
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	4 October 2018

Recommendation *[see also section 3]*

The PRAC considered the available evidence from the preliminary data of an observational study on birth outcomes in HIV-infected women – the Tsepamo study conducted in Botswana, as well as the additional data submitted by the MAH in relation to the safety of use of dolutegravir during pregnancy (from clinical trials, post-marketing experience and literature). The PRAC has agreed that the MAH of dolutegravir containing products – single ingredient and fixed combinations (ViiV Healthcare) should address the below recommendations.

Update of the Product Information

The MAH should submit a variation within 1 month of the publication of the PRAC recommendation, to amend the product information as described below. When more complete data from the Tsepamo study, as well as data from other sources (including the non-clinical studies) become available, the MAH should consider taking the appropriate steps, including submitting further variations as applicable, in order to more fully inform the present understanding about the risk of neural tube defects and the implications of the use of dolutegravir during pregnancy.

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of dolutegravir. WOCBP who are taking dolutegravir should use effective contraception throughout treatment.

Pregnancy

Preliminary data from a surveillance study has suggested an increased incidence of neural tube defects (0.9%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%).

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to

dolutegravir at the time of conception and in early pregnancy. Due to the potential risk of neural tube defects, dolutegravir should not be used during the first trimester unless there is no alternative.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformative and foeto/neonatal negative effects. However, as the mechanism by which dolutegravir may interfere in human pregnancy is unknown, the safety in use during the second and third trimester cannot be confirmed. Dolutegravir should only be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

In animal reproductive toxicology studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3). Dolutegravir was shown to cross the placenta in animals.

Package leaflet

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

Pregnancy

If you are pregnant, if you become pregnant, or if you are planning to have a baby:

-> Talk to your doctor about the risks and benefits of taking {product name}.

Taking {product name} at the time of becoming pregnant or during the first twelve weeks of pregnancy, may increase the risk of a type of birth defect, called neural tube defect, such as spina bifida (malformed spinal cord).

If you could get pregnant while receiving {product name}, you need to use a reliable method of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection), to prevent pregnancy.

Tell your doctor immediately if you become pregnant or are planning to become pregnant. Your doctor will review your treatment. Do not discontinue {product name} without consulting your doctor, as this may harm you and your unborn child.

1.3. Hormonal contraceptives[5] – Suicidality with hormonal contraceptives following a recent publication

Authorisation procedure	Centralised and non-centralised
EPITT No	19144
PRAC rapporteur(s)	Doris Stenver (DK)
Date of adoption	4 October 2018

Recommendation

The PRAC considered that the limitations of the available data did not allow to clearly establish whether there is an increased risk of suicidal thoughts and behaviour associated with the use of hormonal contraceptives. However, it was recognised that depressed mood and depression are known to occur in association with the use of hormonal contraceptives. Depression is serious and can sometimes lead to suicidal thoughts and it was considered important to reflect the potential severity of the condition in the product information for hormonal contraceptives. Therefore, the PRAC has agreed that the MAHs for the hormonal contraceptives products are to 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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Package leaflet

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

Warnings and precautions

Psychiatric disorders:

Some women using hormonal contraceptives including {product name} have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

[5] Chlormadinone, estradiol; chlormadinone acetate, ethinylestradiol ; conjugated estrogens, medrogestone ; conjugated estrogens, medroxyprogesterone acetate; conjugated estrogens, norgestrel; cyproterone, ethinylestradiol; cyproterone acetate, estradiol valerate; desogestrel; desogestrel ,ethinylestradiol; dienogest, estradiol; dienogest, ethinylestradiol; drospirenone, estradiol; drospirenone, ethinylestradiol; estradiol, estriol, levonorgestrel; estradiol, gestodene; estradiol, levonorgestrel; estradiol, medroxyprogesterone acetate; estradiol, nomegestrol acetate; estradiol, norethisterone; estradiol, norgestimate; estradiol (17-beta), progesterone; estradiol (17-beta), trimegestone; estradiol valerate, norgestrel; ethinylestradiol, etonogestrel; ethinylestradiol, etynodiol; ethinylestradiol, gestodene; ethinylestradiol, gestodene; ethinylestradiol, levonorgestrel; ethinylestradiol, lynestrenol; ethinylestradiol, norethisterone; ethinylestradiol, norgestimate; ethinylestradiol, norgestrel; levonorgestrel, ethinylestradiol; ethinylestradiol; levonorgestrel; medroxyprogesterone; mestranol, norethisterone; nomegestrol; nomegestrol acetate, estradiol; norelgestromin, ethinyl estradiol; norethisterone

1.4. Teriflunomide – Dyslipidaemia

Authorisation procedure	Centralised
EPITT No	19227
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	4 October 2018

Recommendation

Having considered the available evidence in EudraVigilance, the literature, clinical trials and the cumulative review by the MAH of Aubagio (Sanofi Genzyme) the PRAC has agreed that the MAH of Aubagio 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

Tabulated list of adverse reactions

Metabolism and nutrition disorders
Frequency 'Not known'': Dyslipidaemia

Package leaflet

4. Possible side effects

Not known (frequency cannot be estimated from the available data)

- abnormal levels of fats (lipids) in the blood

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Avelumab	Pancreatitis (19291)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 1 December 2018)	Merck Europe B.V.
Belimumab	Lupus nephritis (19174)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 October 2018)	Glaxo Group Ltd
Olanzapine	Gestational diabetes (19306)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 12 December 2018)	Eli Lilly Nederland B.V.
Tocilizumab	Facial paralysis (19295)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 12 December 2018)	Roche Registration GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab; infliximab	Risk of lymphoma in patients with inflammatory bowel disease (19121)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	MAHs of adalimumab-containing and infliximab-containing products
Canagliflozin; dapagliflozin; empagliflozin; ertugliflozin	Fournier's gangrene (19308)	Martin Huber (DE)	Provide comments on proposed updates to the product information; provide comments on the need for additional risk minimisation measures, including the need for a Direct Healthcare Professional Communication (DHPC) (submission by 26 October 2018)	Janssen-Cilag International NV, AstraZeneca AB, Boehringer Ingelheim International GmbH, Merck Sharp & Dohme B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C[6]	Dysglycaemia (19234)	Julie Williams (UK)	· See section 1.1 · Monitor cases of hyperglycaemia in PSURs	Bristol-Myers Squibb Pharma EEIG, Gilead Sciences Ireland UC, AbbVie Deutschland GmbH & Co. KG, Merck Sharp & Dohme B.V.
Dolutegravir	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women (19244)	Julie Williams (UK)	· See section 1.2 · Update the risk management plan (RMP) · Monitor pregnancy outcomes in future PSURs and provide supplementary information in the next PSUR (submission by 27 March 2019) and/or following PSURs	ViiV Healthcare B.V.
Hormonal contraceptives	Known association between hormonal contraceptives and a small increase in breast cancer following a recent publication (19143)	Menno van der Elst (NL)	Routine pharmacovigilance	MAHs of hormonal contraceptive-containing products
Oxybutynin; carbamazepine	Drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations	Laurence de Fays (BE)	Routine pharmacovigilance	MAHs of oxybutynin-containing products and carbamazepine-containing products
Trastuzumab; trastuzumab emtansine; pertuzumab	Multiple sclerosis relapse (19208)	Doris Stenver (DK)	Monitor in PSUR	Roche Registration GmbH; Celltrion Healthcare Hungary Kft.; Samsung Bioepis UK Ltd

[6] Daclatasvir; dasabuvir; elbasvir, grazoprevir; glecaprevir, pibrentasvir; ledipasvir, sofosbuvir; ombitasvir, pariteprevir, ritonavir; sofosbuvir; sofosbuvir, velpatasvir; sofosbuvir, velpatasvir, voxilaprevir