

1 October 2018¹
EMA/PRAC/595691/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 3-6 September 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 3-6 September 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 September 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. Alemtuzumab – Cytomegalovirus infection

Authorisation procedure	Centralised
EPITT No	19193
PRAC rapporteur(s)	Anette Kirstine Stark (DK)
Date of adoption	6 September 2018

Recommendation

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

Infections

[...]

Cytomegalovirus (CMV) infections including cases of CMV reactivation have been reported in LEMTRADA-treated patients. Most cases occurred within 2 months of alemtuzumab dosing. Before initiation of therapy, evaluation of immune serostatus could be considered according to local guidelines.

4.8. Undesirable effects

Table 1

Infections and infestations: cytomegalovirus infection - frequency uncommon

Package leaflet

2. What you need to know before you are administered LEMTRADA

Warnings and precautions

Infections

[...]

Infections with a virus called **cytomegalovirus** have been reported in patients treated with LEMTRADA. Most cases occurred within 2 months of alemtuzumab dosing. Tell your doctor right away if you have symptoms of infection such as fever or swollen glands.

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. Possible side effects

Uncommon (may affect up to 1 in 100 people)

- **Infections:** [...], cytomegalovirus infection

1.2. Dimethyl fumarate – Immune thrombocytopenic purpura and thrombocytopenia

Authorisation procedure	Centralised
EPITT No	19192
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	6 September 2018

Recommendation [see also section 3 for immune thrombocytopenic purpura]

Having considered the available evidence in EudraVigilance and in the literature for an association between thrombocytopenia and dimethyl fumarate indicated for the treatment of multiple sclerosis, the PRAC has agreed that the MAH of Tecfidera (Biogen Idec Ltd) 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

Blood and lymphatic system disorders

Frequency 'uncommon': Thrombocytopenia

Package leaflet

4. Possible side effects

Uncommon side effects

These may affect *up to 1 in 100 people*:

- reduction in blood platelets

1.3. Duloxetine – Interstitial lung disease

Authorisation procedure	Centralised and non-centralised
EPITT No	19175
PRAC rapporteur(s)	Pilar Rayón (ES)
Date of adoption	6 September 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature for an association of duloxetine with interstitial lung disease, the PRAC has agreed that the MAH(s) of duloxetine-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

Tabulated list of adverse reactions

Respiratory, thoracic and mediastinal disorders

Frequency 'rare': Interstitial lung disease^X

^XEstimated frequency based on placebo-controlled clinical trials

and

Frequency 'rare': Eosinophilic pneumonia^Y

^YEstimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

Package leaflet

4. Possible side effects

Rare side effects (may affect up to 1 in 1000 people)

[...]

Coughing, wheezing and shortness of breath which may be accompanied by a high temperature

1.4. Fluoroquinolones for systemic and inhaled use⁴ – Aortic aneurysm and dissection

Authorisation procedure	Centralised and non-centralised
EPITT No	18651
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	6 September 2018

Recommendation [see also section 3]

Having considered the evidence from epidemiological (Lee et al. 2015, Daneman et al. 2015, Pasternak et al. 2018) and non-clinical studies (LeMaire et al. 2018), and the responses from the MAHs of fluoroquinolones, the PRAC has agreed that the MAHs of fluoroquinolones for systemic and inhaled use should submit a variation within 3 months, to amend the product information as described below (new text underlined).

Summary of product characteristics

4.4. Special warnings and precautions for use

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Package leaflet

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

Warning and precautions

Talk to your doctor before taking [product]:

[...]

- if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).

- if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).

- if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-

⁴ Ciprofloxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin.

Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis).

[...]

If you feel sudden, severe pain in your abdomen, chest or back, go immediately to an emergency room.

1.5. Hydrochlorothiazide – Skin cancer

Authorisation procedure	Centralised and non-centralised
EPITT No	19138
PRAC rapporteur(s)	Kirsti Villikka (FI)
Date of adoption	6 September 2018

Recommendation [see also section 3]

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered there was a biologically plausible mechanistic model supporting the increased risk of non-melanoma skin cancer (NMSC) following higher cumulative doses of hydrochlorothiazide (HCTZ). Therefore, the PRAC has agreed that the MAHs for the hydrochlorothiazide-containing 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

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

5.1. Pharmacodynamic properties

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4).

Package leaflet

2. What you need to know before you take X

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or> <nurse> before <taking> <using> X

- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while <taking> <using> X

4. Possible side effects

Frequency 'not known': Skin and lip cancer (Non-melanoma skin cancer)

1.6. Ipilimumab – Cytomegalovirus gastrointestinal infection

Authorisation procedure	Centralised
EPITT No	19207
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	6 September 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH of ipilimumab 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

Immune-related gastrointestinal reactions:

[...]

Patients must be monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation. Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. ~~Diarrhoea or colitis occurring after initiation of ipilimumab must be promptly evaluated to exclude infectious or other alternate etiologies.~~ In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration. Post-marketing cases of cytomegalovirus (CMV) infection/reactivation have been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate etiologies.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per NCI-CTCAE v4 severity grading classification). Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected mild to moderate colitis (e.g. abdominal pain or blood in stools) may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of ipilimumab should be withheld and corticosteroid therapy (e.g. prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, ipilimumab may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and systemic high-dose intravenous corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. In clinical trials, rapid tapering (over periods < 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.

The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. ~~However, a~~ Addition of an alternative immunosuppressive agent to the corticosteroid regimen may should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including Cytomegalovirus (CMV) infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial and parasitic etiology) be considered. In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected (see the Summary of Product Characteristics for infliximab).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban	Pancreatitis (19265)	Menno van der Elst (NL)	Supplementary information requested (submission by 7 November 2018)	Bristol-Myers Squibb / Pfizer EEIG
Denosumab	Alopecia (18332)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 5 December 2018)	Amgen Europe B.V.
Fingolimod	Autoimmune haemolytic anaemia (19260)	Ghania Chamouni (FR)	Assess in the next PSUR (submission by 9 May 2019)	Novartis Europharm Limited
Gabapentin	Dysphagia (19296)	Martin Huber (DE)	Supplementary information requested (submission by 7 November 2018)	Pfizer
Nivolumab	Scleroderma (19282)	Brigitte Keller-Stanislaws ki (DE)	Supplementary information requested (submission by 7 November 2018)	Bristol-Myers Squibb Pharma EEIG
Pazopanib	Rhabdomyolysis (19281)	Doris Irene Stenver (DK)	Assess in the next PSUR (submission by 27 December 2018)	Novartis Europharm Limited
Pemetrexed	Syncope (19289)	Ghania Chamouni (FR)	Assess in the ongoing PSUSA procedure EMEA/H/C/PSUSA/0000 2330/201802 (submission by 5 September 2018)	MAHs for pemetrexed containing products which have submitted a PSUR during the PSUSA procedure EMEA/H/C/PSUSA/00002330/201802
Rivaroxaban	Premature ending of the GALILEO study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement (TAVR) (19294)	Ulla Wändel Liminga (SE)	- Supplementary information requested (submission by 11 April 2019) - Circulate a Direct Healthcare Professional Communication (DHPC)	Bayer AG

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sunitinib	Aortic dissection (19283)	Amelia Cupelli (IT)	Assess in the ongoing PSUSA procedure EMEA/H/C/PSUSA/0000 2833/201804 (submission by 31 October 2018)	Pfizer Limited
Tocilizumab	Psoriasis (19273)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 November 2018)	Roche Registration GmbH
Voriconazole	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19276)	Menno van der Elst (NL)	Assess in the ongoing PSUSA procedure EMEA/H/C/PSUSA/0000 3127/201802 (submission by 5 September 2018)	Pfizer Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Clomipramine; Serotonin and noradrenaline reuptake inhibitors (SNRI) ⁵ ; selective serotonin reuptake inhibitors (SSRI) ⁶ ; vortioxetine	Persistent sexual dysfunction after drug withdrawal (19277)	Menno van der Elst (NL)	No action at this stage	Not applicable
Dimethyl fumarate	Immune thrombocytopenic purpura and thrombocytopenia (19192)	Martin Huber (DE)	- See section 1.2 - Routine pharmacovigilance for immune thrombocytopenic purpura	Biogen Idec Ltd

⁵ Desvenlafaxine; duloxetine; milnacipran; venlafaxine

⁶ Citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Fluoroquinolones for systemic and inhaled use ⁷	Aortic aneurysm and dissection (18651)	Martin Huber (DE)	• See section 1.4 • Circulate a Direct Healthcare Professional Communication (DHPC)	MAHs of fluoroquinolones for systemic and inhaled use ⁵
Hydrochlorothiazide	Skin cancer (19138)	Kirsti Villikka (FI)	• See section 1.5 • Circulate a Direct Healthcare Professional Communication (DHPC)	MAHs of hydrochlorothiazide-containing products
Olanzapine	Somnambulism (19202)	Kimmo Jaakkola (FI)	Monitor in PSUR	MAHs of olanzapine-containing products
Sildenafil	Pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction (19287)	Menno van der Elst (NL)	Circulate a Direct Healthcare Professional Communication (DHPC)	Pfizer Europe MA EEIG
Sitagliptin; sitagliptin, metformin hydrochloride	Potential drug interaction between sitagliptin and angiotensin-converting-enzyme (ACE)-inhibitors leading to an increased risk of angioedema (17608)	Menno van der Elst (NL)	Routine pharmacovigilance	MAH of sitagliptin-containing products

⁷ Ciprofloxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin.