1 October 2018[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 3-6 September 2018 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Alemtuzumab – Cytomegalovirus infection (EPITT no 19193)

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

[1] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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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.

4. Possible side effects

Uncommon (may affect up to 1 in 100 people)

Infections: […], cytomegalovirus infection

2. Dimethyl fumarate (Tecfidera) – Immune thrombocytopenic purpura and thrombocytopenia (EPITT no 19192)

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

3. Duloxetine – Interstitial lung disease (EPITT no 19175)

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Respiratory, thoracic and mediastinal disorders

Frequency 'rare': Interstitial lung disease[X]

[X]Estimated frequency based on placebo-controlled clinical trials

and

Frequency 'rare': Eosinophilic pneumonia[Y]

[Y]Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

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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

4. Fluoroquinolones for systemic and inhaled use[2] – Aortic aneurysm and dissection (EPITT no 18651)

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).

[2] Ciprofloxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin.

- 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-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.

5. Hydrochlorothiazide – Skin cancer (EPITT no 19138)

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 (≥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 (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~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)

6. Ipilimumab – Cytomegalovirus gastrointestinal infection (EPITT no 19207)

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.

[…]

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).