21 May 2015
EMA/PRAC/274321/2015
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 4-7 May 2015

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 4-7 May 2015 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] 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 (18-21 May 2015) 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] The relevant EPITT reference number should be used in any communication related to a signal.

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The established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

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[2]

1.1. Fingolimod – Progressive Multifocal Leukoencephalopathy (PML)

Substance (invented name)	Fingolimod (Gilenya)
Authorisation procedure	Centralised
EPITT No	18241
PRAC rapporteur(s)	Arnaud Batz (FR)
Date of adoption	7 May 2015

Recommendation

Having considered the available evidence, including data submitted by the Marketing Authorisation Holder (MAH), and taking into account that Progressive Multifocal Leukoencephalopathy (PML) is a complex disease which may take a prolonged time before becoming clinically symptomatic, the PRAC has agreed that an update of the product information is warranted. Therefore, the MAH for fingolimod should submit a variation within 2 months, to amend the product information as described below (new text underlined) and to include PML in the RMP as an important identified risk (under the risk of infections). The prescriber's guide should be updated with this risk and PML should also be closely monitored in future PSURs.

The PRAC agreed to ask for a scientific advisory group (SAG) advice regarding the risk factors and the monitoring (e.g. MRI, JCV status, CD4+/CD8+ ratio) of the patients treated with fingolimod, in order to advise on possibilities to improve the prognosis of the patients diagnosed early, and to identify patients at risk of developing PML.

Summary of Product Characteristics:

Section 4.4 – Special warnings and precautions for use

Infections

[…]

Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorization (see section 4.8). PML is an opportunistic infection caused by John-Cunningham virus (JCV) which may be fatal or result in severe disability. During routine MRI, physicians should pay attention to PML suggestive lesions. In case of PML is suspected, treatment with fingolimod should be discontinued.

Section 4.8 - Undesirable effects

Infections and infestations

Frequency "not known": Progressive multifocal leukoencephalopathy (PML)

[2] Translations in EU languages of the adopted PRAC recommendations for update of the product information are also available to MAHs on the EMA website.

Package Leaflet:

Section 4: Possible side effects

Some side effects could be or could become serious

[…]

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

Risk of a rare brain infection called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to an MS relapse. Symptoms may include new or worsening weakness on one side of the body: clumsiness, changes in vision, speech, thinking, or memory; or confusion or personality changes lasting for more than several days.

1.2. Latanoprost (Xalatan) – Increased reporting of eye disorders, in particular eye irritation, after change of formulation

Substance (invented name)	Latanoprost (Xalatan)
Authorisation procedure	Non-centralised
EPITT No	18068
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	7 May 2015

Recommendation

Having considered the available evidence from spontaneous reports, EudraVigilance and the literature, the PRAC considers that patients receiving Xalatan should be warned about the importance of seeking medical advice if they experience excessive eye irritation. Therefore the MAH for Xalatan (latanoprost) should submit a variation within 2 months to update the Package Leaflet as described below (new text underlined).

Section 4:

• Eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye).

If you experience eye irritation severe enough to make your eyes water excessively, or make you consider stopping this medicine, talk to your doctor, pharmacist or nurse promptly (within a week). You may need your treatment to be reviewed to ensure you keep receiving appropriate treatment for your condition.

Furthermore, the MAH should continue to monitor events of eye irritation and present updated data in the next PSUR. A targeted questionnaire should be implemented to maximise the information obtained from future cases.

1.3. Leflunomide – Colitis (EPITT no 18189)

Substance (invented name)	Leflunomide (Arava, Repso, Leflunomide Winthrop, Leflunomide medac, Leflunomide ratiopharm)
Authorisation procedure	Centralised
EPITT No	18189
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	7 May 2015

Recommendation

Having considered the available evidence from clinical trials (colitis reported in 1% to <3% in treatment arm), from spontaneous cases including reported positive de-challenge and re-challenge cases as well as supporting reports in literature, the PRAC has agreed that the MAH(s) of leflunomide-containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Summary of Product Characteristics:

Section 4.4 – Special warning and precautions for use:

Colitis, including microscopic colitis has been reported in patients treated with leflunomide. In patients on leflunomide treatment presenting unexplained chronic diarrhoea appropriate diagnostic procedures should be performed.

Section 4.8 – Undesirable effects:

Gastrointestinal disorders

Frequency 'common': Colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis.

Package Leaflet:

Section 2: What you need to know before you take Arava

Warning and precautions

Tell your doctor if you have unexplained chronic diarrhoea. Your doctor may perform additional tests for differential diagnosis.

Section 4: Possible side effects

Frequency 'common': colitis

1.4. Natalizumab – Anaemia

Substance (invented name)	Natalizumab (Tysabri)
Authorisation procedure	Centralised
EPITT No	18137
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	7 May 2015

Recommendation

Having considered the data submitted by the MAH, as well as the evidence from EudraVigilance cases and the literature, the MAH of Tysabri should submit a variation within 60 days to add “anaemia” and “haemolytic anaemia” to section 4.8 of the SmPC and to update the Package Leaflet accordingly. The frequency may be calculated by considering the frequency of anaemia and haemolytic anaemia in studies.

2. Recommendations for submission of supplementary information

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a **causal relationship** between the medicine and the reported adverse event.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amikacin	Drug reaction with eosinophilia and systemic symptoms (DRESS) (18304)	Maia Uusküla (EE)	Supplementary information requested (submission by 11/07/2015)	Bristol Myers Squib
Decitabine	Organising pneumonia (18303)	Arnaud Batz (FR)	Assess in the next PSUR (submission by 10/07/2015)	Janssen-Cilag International N.V.
Lenalidomide	Pulmonary alveolar haemorrhage (18300)	Arnaud Batz (FR)	Supplementary information requested (submission by 11/07/2015)	Celgene Europe Limited
Long acting GLP-1 agonists (liraglutide)	Medullary thyroid cancer (18292)	Menno van der Elst (NL)	Supplementary information requested (submission by 11/07/2015)	Novo Nordisk A/S
Mitotane	Sex hormone disturbances and development of ovarian macrocysts (18301)	Dolores Montero Corominas (ES)	Supplementary information requested (submission by 11/07/2015)	Laboratoire HRA Pharma
Rivaroxaban	Pulmonary alveolar haemorrhage (18291)	Yue Qun-Ying (SE)	Assess in the next PSUR (submission by 24/11/2015)	Bayer Pharma AG
Tamsulosin	Urinary incontinence (18317)	Sabine Straus (NL)	Supplementary information requested (submission by 11/07/2015)	Astellas Pharma

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Angiotensin-converting enzyme (ACE)-inhibitors: benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, zofenpril	Hallucinations (18286)	Menno van der Elst (NL)	Routine pharmacovigilance	MAHs of ACE-inhibitors containing products
Digoxin	Mortality in patients with atrial fibrillation (18259)	Carmela Macchiarulo (IT)	No action at this stage	Not applicable
Olanzapine	Angle closure glaucoma (18159)	Terhi Lehtinen (FI)	Routine pharmacovigilance	Eli Lilly Nederland B.V.
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG, Baxter AG, Pfizer Limited, various
Sildenafil	Pulmonary haemorrhage in off label paediatric use (18183)	Menno van der Elst (NL)	Update RMP and monitor in PSUR	Pfizer Limited