21 May 2015
EMA/PRAC/277134/2015
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals for update of product information

Adopted at the 4-7 May 2015 PRAC

1. Fingolimod – Progressive Multifocal Leukoencephalopathy (PML) (EPITT no 18241)

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 (SmPC):

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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5525
Send a question via our website www.ema.europa.eu/contact

Section 4.8 - Undesirable effects

Infections and infestations

Frequency “not known”: Progressive multifocal leukoencephalopathy (PML)

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.

2. Latanoprost (Xalatan) – Increased reporting of eye disorders, in particular eye irritation, after change of formulation (EPITT no 18068)

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.

3. Leflunomide – Colitis (EPITT no 18189)

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).

SmPC:

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

4. Natalizumab – Anaemia (EPITT no 18137)

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.