11 April 2019
EMA/PRAC/218935/2019

PRAC List of questions

To be addressed by the marketing authorisation holder

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1483

Lemtrada EMEA/H/A-31/1483/C/3718/0028

INN/active substance: alemtuzumab

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The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1

Please provide information on the estimated patient exposure to alemtuzumab in the different EEA Member States and worldwide. This should include data from ongoing and completed clinical trials, non-interventional studies and post-marketing sources stratified by number of treatment cycles. An overview of the approved indication(s) worldwide should also be provided.

Question 2

Please provide cumulative reviews of all cardiovascular adverse events occurring within 30 days of an infusion of Lemtrada from all sources (clinical trials, non-interventional studies, literature and spontaneous reports). The data should be stratified by number of cycles.

a. The analyses should include but not be limited to frequency and seriousness (outcome), time to onset of first symptoms since last dose for cardiac ischaemia and myocardial infarction, ischaemic and haemorrhagic stroke, arterial dissection, pulmonary haemorrhage and embolism, vascular dissection, vasculitis and thrombocytopenia. Detailed information on individual cases should be presented (narrative and tabulated format). Information on the background rate of the event in the population of relapsing remitting multiple sclerosis should be provided.

b. Please discuss potential clusters/similarities potential confounders such as concomitant diseases and medications. Potential risk factors such as concomitant infusion reactions with bradycardia / tachycardia, hypo- or hypertension or ECG abnormalities, should be assessed.

c. The potential pathomechanisms of the cardiovascular events should be discussed and experience with alemtuzumab in other indications should be considered. This should include but not be limited to a discussion of a possible mechanistic relation of hypertension, vasculitis and immediate thrombocytopenia in cardiovascular reactions (e.g. myocardial infarction, stroke, arterial dissection and pulmonary haemorrhage). Relevant publications such as the one by Azevedo et al.[1] should be discussed.

Question 3

Please provide a cumulative review from all sources (clinical trials, non-interventional studies, literature and spontaneous reports) of the following immune mediated diseases by analysing frequency/incidence, risk factors, time to onset, seriousness and potential pathophysiological mechanisms of the immune-mediated adverse events. Detailed information on individual cases should be presented (narrative and tabulated format):

a. Hepatic injury / autoimmune hepatitis

b. Autoimmune-mediated CNS disease

c. Guillain–Barré syndrome (GBS)

Information on the background rate of the event in the population of relapsing remitting multiple sclerosis should be provided.

[1] *Azevedo CJ, Kutz C, Dix A, Boster A, Sanossian N, Kaplan J. Intracerebral haemorrhage during alemtuzumab administration. Lancet Neurol. 2019;unk:1-3. doi:10.1016/S1474-4422(19)30076-6.*

Question 4

Please provide a thorough cumulative review and causality assessment of fatal cases reported for Lemtrada for the indication multiple sclerosis from all sources (clinical trials, non-interventional studies, literature and spontaneous reports). Detailed information on individual cases should be presented (narrative and tabulated format).

a. The MAH is asked to stratify fatal cases according to number of infusions and time on treatment. The MAH should comment on any cluster with regard to dosing and time on treatment.

b. The analysis should include a review of the cause(s) that lead to death.

c. When available the MAH should provide information on previous multiple sclerosis treatments.

The MAH is asked to calculate the case fatality rate. The fatality rate should be calculated separately for ongoing and completed clinical trials, non- interventional studies and post-marketing sources stratified by region. Information on the background rate in the population of relapsing remitting multiple sclerosis should be provided.

Question 5

Based on the review undertaken, please discuss the need and feasibility for risk minimization measures addressing the risks above, including changes of the product information, as well as the monitoring of their effectiveness. Please also discuss communication activities (e.g. DHPC), as appropriate.

Question 6

Taking all the available data into account, the MAH should provide a comprehensive discussion of the benefit-risk balance of the product in the authorised therapeutic indication and, considering the new information on risks, describe the circumstances in which the use of alemtuzumab in adult patients with relapsing remitting multiple sclerosis could be justified.