Annex IV

Scientific conclusions

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Background information

During the assessment of the periodic safety update report (PSUSA) for Lemtrada (EMEA/H/C/PSUSA/00010055/201809), the following new emerging and serious safety concerns were highlighted in addition to the known safety profile of alemtuzumab, which raised major concerns to the Pharmacovigilance Risk Assessment Committee (PRAC):

- Fatal cases: Several fatal cases were identified during the PSUSA procedure, which indicate that the current recommendations for monitoring may be insufficient.

- Cardiovascular adverse events in close temporal association with Lemtrada infusions (e.g. cardiac ischaemia and myocardial infarction, ischaemic and haemorrhagic stroke, arterial dissection, pulmonary haemorrhage and embolism, vasculitis and thrombocytopenia), including a possible mechanistic relation to these adverse events.

- Immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre Syndrome (GBS).

Limited information, including lack of detailed information on the individual cases, was available on these concerns during the PSUSA assessment, precluding a thorough evaluation.

On 10 April 2019 the European Commission (EC) therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data and requested the PRAC to assess the above safety concerns and their impact on the benefit-risk balance of Lemtrada and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Provisional measures were introduced at the start of procedure to protect patients while the detailed evaluation was ongoing. As a provisional measure, it was recommended that *new treatment with Lemtrada should only be initiated in adult patients with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments, or in adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.*

Overall summary of the scientific evaluation by the PRAC

The efficacy of alemtuzumab in relapsing remitting multiple sclerosis patients across multiple parameters of the disease is well established and maintained over long term follow up. This level of efficacy is present across a wide range of patient populations, as evidenced by the consistency of findings across various subgroups of participants in alemtuzumab clinical studies.

As part of the current review, a number of serious, life-threatening and disabling risks associated with Lemtrada have been assessed. Acute coronary syndrome and cerebrovascular events including arterial dissection and haemorrhagic stroke, pulmonary haemorrhage and transient thrombocytopenia have been identified as risks in close temporal association with the infusion of alemtuzumab. These risks are considered to be related to cytokine release syndrome, which has been described in the literature for alemtuzumab[1,2].

[1] Wing MG et al. Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin Invest 1996;98(12):2819-2826

Following the review, it has been reconfirmed that Lemtrada causes secondary autoimmune disease including auto-immune hepatitis, thyroiditis, immune thrombocytopenic purpura, acquired haemophilia A, nephropathies, cytopenias and serious immunological reactions such as haemophagocytic lymphohistiocytosis. Cases of poly-autoimmunity associated with Lemtrada have also been identified.

During the procedure, other new adverse reactions were identified which are also considered related to Lemtrada such as Epstein-Barr virus re-activation.

One general characteristic of alemtuzumab which impacts on its safety profile and on risk management is the very long treatment effect, and thereby the infrequent administration regimen. Thus, due to the long term effect of alemtuzumab, treatment discontinuation has limited value from a risk management perspective.

No surrogate or biomarker for patients at risk for serious cytokine release or autoimmunity was identified. Therefore many of the newly-identified risks associated to Lemtrada are unpredictable and largely unavoidable. In such circumstances it is necessary to restrict use of the alemtuzumab to patients who can benefit the most from treatment and who may be ready to accept the serious risks associated with treatment. This includes not just a restricted therapeutic indication but also contraindications in subpopulations anticipated, due to risk factors, to be at higher risk of developing the serious adverse reactions.

In this context, and taking also into account the advice of the SAG, PRAC concluded that Lemtrada should be indicated as a single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

With this conclusion, PRAC acknowledges that early initiation of high-efficacy DMTs in patients with highly active (aggressive) or rapidly evolving RRMS is increasingly viewed as a strategy to prevent or postpone irreversible damage that occurs early in the disease course[3]. Recent studies of RRMS with long-term follow-up have shown that disease-modifying therapies (DMTs) reduce the proportion of patients who progress to SPMS compared to the proportion of untreated patients who progress.

Furthermore, when selecting the most appropriate and effective treatment for the patient, the safety profile and the possibility to manage risks effectively should also be taken into consideration. Vulnerable patient groups such as patients with severe active infections until complete resolution, uncontrolled hypertension, a history of arterial dissection of the cervicocephalic arteries, of stroke, angina pectoris or myocardial infarction and patients with known coagulopathy, on anti-platelet or anti-coagulant therapy, should be contraindicated. Patients with other concomitant autoimmune diseases (besides MS) should also be contraindicated to minimise the risk of development of additional autoimmune disorders.

In order to ensure adequate monitoring of patients before, during and after the infusion of alemtuzumab, rapid diagnosis and prompt and adequate treatment of the above mentioned risks, the infusion of alemtuzumab should take place in a hospital with availability of experts and adequate

[2] Thomas K, Eisele J, Rodriguez-Leal FA, Hainke U, Ziemssen T. Acute effects of alemtuzumab infusion in patients with active relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm. 2016 Apr 29;3(3):e228

[3] Fernandez O et al, 2017 Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? Mult Scler Relat Disord. 2017 Oct;17:75-83.

equipment to manage the risks. The MAH proposed to include also specialised infusion centres with ready access to intensive care. Specialists from other medical disciplines (e.g. cardiologists) and equipment for timely diagnosis and management of adverse reactions however requires, in the view of PRAC, a hospital setting. The PRAC considered a recommendation for a longer follow-up period in hospital (for up to 5 days after the last infusion) to allow for prompt identification and management of serious adverse reactions that may occur. However it was ultimately considered that this long hospitalisation may not be feasible and that, as highlighted by the SAG, there is limited data to indicate it will have a substantial impact in the management of post-infusion adverse reactions.

New infusion instructions are also proposed to allow early identification and management of serious adverse reactions temporally associated with infusion. In addition to close monitoring of cardiovascular function before, during and after the infusion, this also includes new recommendations for platelet count measurement during the infusion cycle and for post-infusion monthly liver transaminase testing.

Currently, safety follow-up of patients is recommended from initiation of the first treatment course and until 48 months after the last treatment course. However, in individual cases autoimmune conditions may occur or be diagnosed later so healthcare professionals should be aware of this possibility.

Cases of pulmonary embolism, vasculitis, central nervous system autoimmune disease and Guillain-Barre Syndrome (GBS) have been reported. The current evidence is insufficient to conclude on a causal relationship with Lemtrada. There are uncertainties about a potential causal relationship with a number of other autoimmune adverse events reported in temporal association with Lemtrada, and these will have to continue to be closely monitored in the future.

In future PSURs, the MAH is expected to submit cumulative reviews and discuss the following safety concerns: vasculitis, CNS inflammation, GBS, diabetes type 1, myasthenic syndrome, myositis, sarcoidosis, GBS, pneumonitis and EBV hepatitis.

A matter of concern is the post-marketing reporting rate of fatalities, including those with short latency after alemtuzumab infusion. The relative young age of patients who died within a short period (30 days) from Lemtrada treatment is also noted. A post authorisation safety study is needed to address these concerns.

A study is also needed to assess the effectiveness of the risk minimisation measures adopted during this review. Considering the serious and unpredictable nature of the newly-identified adverse reactions, it is important to understand whether the newly implemented measures are adhered to in clinical practice.

The MAH for Lemtrada will also disseminate a DHPC to inform healthcare professionals of the outcome of this review, and the educational material for both healthcare professionals and patients will be updated.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable subject to changes to the product information, the educational materials and additional pharmacovigilance activities described above. As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for Lemtrada.

Grounds for PRAC recommendation

Whereas

- PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Lemtrada.

- PRAC reviewed data currently available from post-marketing setting and from clinical trials on fatal cases, cardiovascular adverse events in close temporal association with Lemtrada infusions and immune-mediated diseases, including data provided in writing and at an oral explanation. PRAC also considered the views expressed by the neurology scientific advisory group.
- PRAC concluded that myocardial ischaemia, myocardial infarction, haemorrhagic stroke, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage and thrombocytopenia may occur in close temporal association with the infusion of Lemtrada. PRAC also concluded that alemtuzumab is associated with immune-mediated diseases such as autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH), which can happen with a delay of months to years after the latest treatment. PRAC noted that these risks, which are serious and which can in some cases have a fatal outcome, are largely unpredictable.
- As a consequence, PRAC recommended that treatment with Lemtrada should be restricted to patients with highly active relapsing remitting multiple sclerosis for the following patient groups:
    - patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or
    - patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
- Lemtrada should also be contraindicated in patients with:
    - severe active infections until complete resolution,
    - uncontrolled hypertension,
    - history of arterial dissection of the cervicocephalic arteries,
    - history of stroke,
    - history of angina pectoris or myocardial infarction,
    - coagulopathy, on antiplatelet or anti-coagulant therapy
    - concomitant autoimmune diseases other than multiple sclerosis.
- Furthermore, PRAC recommended that Lemtrada should only be administered in a hospital setting with ready access to intensive care.
- PRAC also made additional recommendations for monitoring of patients before, during and after infusion to ensure timely diagnosis and management of adverse reactions.
- The PRAC considered that given the serious and unpredictable nature of the risks, and that effective risk minimisation is key to support a positive benefit-risk balance, a drug utilisation study is necessary to assess effectiveness of risk minimisation measures.
- PRAC also considered that the data currently available on mortality incidence is limited and therefore the MAH shall investigate the incidence of mortality in patients treated with Lemtrada compared with a relevant patient population.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable subject to changes to the product information, the educational materials and additional pharmacovigilance activities described above.

As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for Lemtrada.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.