16 April 2019
EMA/249094/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report on provisional measures

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

Lemtrada

INN/active substance: alemtuzumab

Procedure number: EMEA/H/A-20/1483/C/3718/0028

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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.

Limited information, including lack of detailed information on the individual cases, precluded a thorough evaluation of their impact on the benefit risk of Lemtrada in view of the time constraints for the PSUSA assessment.

In view of the above, the European Commission (EC) initiated on 11 April 2019 a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Agency to assess the above safety concerns and their impact on the benefit-risk balance for the centrally authorised medicinal product Lemtrada. The EC requested the Agency to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

In addition, the EC requested the Agency to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of this medicinal product.

2. Scientific discussion

2.1. Introduction

Lemtrada (alemtuzumab) is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features. Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system that is characterized by inflammation, demyelination and neuronal loss. Both T and B lymphocytes are involved in the pathogenesis of MS. Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes. The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown but may involve immunomodulation through the depletion and repopulation of lymphocytes.

2.2. Data on safety

During the assessment procedure of the periodic safety update report (PSUSA) for Lemtrada covering the period between 13 September 2017 and 12 September 2018, limited information was available on new emerging and serious safety concerns, including lack of detailed information on the individual cases, precluding a thorough evaluation. These safety concerns are related to:

- **Cardiovascular (including cerebrovascular) reactions temporally associated with alemtuzumab administration**

Several cases with various cardiovascular reactions with close temporal relationship with alemtuzumab administration were identified. Many of those were life-threatening or fatal.

These were five cases of pulmonary alveolar haemorrhage, without apparent confounding, where time to onset (TTO) from the last infusion was 1 day.

Ten post-marketing cases of myocardial infarction with troponin increase were reported. The TTO ranged between 0 and 2 days after the last alemtuzumab infusion. The MAH found that five of the cases were confounded, however in two of the cases the only confounding factor mentioned was the standard pre-treatment with methylprednisolone. In five cases, no apparent confounders were present.

There were also 6 cases of cervicocephalic (vertebral and carotid) dissection, where 4 of these 6 cases had a noticeable short time to onset within 3 days from the last alemtuzumab infusion.

Eight cases of a cerebrovascular accident in close temporal association with Lemtrada administration were reviewed. Six patients experienced a hemorrhagic stroke and two patients had an ischaemic stroke. The TTO (from the last infusion) was 1 day. It is noticed that an additional five cases of haemorrhagic stroke have been published in 2019. The patients had no risk factors and developed first symptoms several hours after leaving the infusion centre.

Common to these cardiovascular reactions was a close temporal relationship to an alemtuzumab infusion, as the majority of cases occurred during the treatment course or within 1-3 days after the last infusion. This temporal relationship to alemtuzumab infusions is suggestive of a causal association. It is noted that in some cases increase of blood pressure was documented. According to existing recommendations, observation for infusion associated reactions (IARs) should be undertaken during and for two hours after infusion. Despite these recommendations, in the majority of cases it was not possible to predict these cardiovascular reactions prior to hospital discharge, and reactions occurred outside a hospital setting. It is therefore questioned whether the current risk minimisation measures are able to mitigate the risk of occurence of these cardiovascular reactions.

- **Immune-mediated reactions**

Autoimmune disorders are an important identified risk for alemtuzumab. New life-threatening and potentially fatal immune-mediated reactions were identified.

Seven cases of Haemophagocytic lymphohistocytosis (HLH) were identified. HLH is a life-threatening condition of severe hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages. The temporal onset corresponded to the time of reconstitution of the immune system after depletion of B- and T-lymphocytes following Lemtrada treatment.

In addition, several cases of autoimmune hepatitis (AIH) including fatalities were reported.

The cases of HLH and AIH suggest that despite the recommendations for intensive monitoring and alertness to immune-mediated reactions until 48 months following last treatment course, it has not

been possible to take adequate measures to detect them early enough. Thus, it is questioned whether the current risk minimisation measures are effective.

Literature reports[1, 2, 3] have highlighted B-cell mediated central nervous system (CNS) lesions with temporal onset of 6 months after infusion of alemtuzumab. These cases are characterised by specific MRI lesions and unexpected high total B cell count which may suggest a B-cell-mediated activation of disease. On this basis, the authors of the papers hypothesise that an autoimmune reaction could be directed at CNS in rare cases.

- **Fatal cases**

Several of the serious risks in relation to alemtuzumab resulted in fatal outcomes despite monitoring of the patients and adherence to the current risk minimisation measures such as pre-medication.

3. Benefit-risk balance

Although efficacy of alemtuzumab in RRMS patients is well established, these emerging and serious safety concerns may impact the benefit-risk balance of Lemtrada.

In addition, there are serious doubts as to whether the risk minimisation measures currently in place are sufficient to adequately manage the risks associated to alemtuzumab in the current target population.

In view of the seriousness of the events observed and until a thorough review of the data is finalised, it is appropriate to limit exposure of new patients to alemtuzumab by introducing amendments to the product information.

Therefore PRAC 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.

4. Risk management

4.1. Risk minimisation activities

4.1.1. Amendments to the product information

The following restriction was introduced in annex II of the Product Information as a provisional measure while the review is ongoing:

New treatment 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

1 Haghikia A et al. Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy. Lancet Neurol. 2017 Feb;16(2):104-106

2 Wehrum et al., Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology. 2018 Feb ;90(7): e601-e605

3 Willis M et al., An observational study of alemtuzumab following fingolimod for multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2017 Jan;4(2): e320

treatments, or in adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.

In addition, the PRAC considered important that the risk minimisation measures recommended within the assessment of the PSUSA procedure (EMEA/H/C/PSUSA/00010055/201809) are implemented together with the provisional measures. These changes include amendments to:

- section 4.4 of the SmPC to add warnings related to serious reactions temporally associated with alemtuzumab infusion including pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection, as well as warnings on autoimmune hepatitis, hepatic injury and haemophagocytic lymphohistiocytosis.
- Section 4.8 of the SmPC to add the adverse reactions pulmonary alveolar haemorrhage, haemophagocytic lymphohistiocytosis, myocardial infarction, stroke (including ischemic and haemorrhagic stroke), cervicocephalic arterial dissection and neutropenia.

The Package Leaflet was amended accordingly.

4.1.2. Direct Healthcare Professional Communications/Communication plan

A DHPC was adopted by PRAC to communicate the warnings and restrictions described above to healthcare professionals.

5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Lemtrada, in particular the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004, taking into account the grounds set out in Articles 116 of Directive 2001/83/EC.
- The PRAC reviewed the available data on cardiovascular reactions, including data provided by the marketing authorisation holder in the context of the PSUSA procedure. Several cases with various cardiovascular reactions were identified, including pulmonary alveolar haemorrhage, myocardial infarction, and ischaemic and haemorrhagic stroke as well as arterial dissection. Many of these cases were life-threatening or fatal. Common to these cardiovascular reactions was a close temporal relationship to an alemtuzumab infusion, which is suggestive of a causal association.
- The PRAC also reviewed the available data on immune-mediated adverse events, including data provided by the marketing authorisation holder in the context of the PSUSA procedure. New life-threatening and potentially fatal immune-mediated adverse reactions were identified, including haemophagocytic lymphohistocytosis and autoimmune hepatitis. The PRAC also noted that recent literature reports have highlighted B-cell mediated central nervous system (CNS) lesions with temporal onset of 6 months after infusion of alemtuzumab.
- In addition, several fatal cases were identified both in the literature and in the Eudravigilance database. Information from some fatal cases indicates that current recommendations for monitoring may be insufficient.

- The PRAC noted that although efficacy of alemtuzumab in relapsed remitting multiple sclerosis patients is well established, these emerging and serious safety concerns can impact the benefit-risk balance of Lemtrada, and that until a thorough review is finalised, it would be appropriate as a provisional measure to limit the patients exposed to alemtuzumab. Therefore, in view of the seriousness of the events observed, the PRAC recommended provisional amendments to the product information to restrict use of alemtuzumab in new patients to adults with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments, or to adults with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.
- In addition the PRAC considered important that the risk minimisation measures recommended within the assessment of the current PSUSA procedure are also implemented together with the provisional measures. The PRAC recommended as part of the PSUSA procedure the addition of warnings related to serious reactions temporally associated with alemtuzumab infusion including pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection. New warnings on autoimmune hepatitis, hepatic injury and haemophagocytic lymphohistiocytosis are also added. Furthermore, the following new adverse reactions are added: pulmonary alveolar haemorrhage, haemophagocytic lymphohistiocytosis, myocardial infarction, stroke (including ischemic and haemorrhagic stroke), cervicocephalic arterial dissection and neutropenia.

In view of the above, the Committee considers that the benefit-risk balance of Lemtrada (alemtuzumab) remains favourable subject to the agreed provisional amendments to the product information. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Lemtrada (alemtuzumab).

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.