NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) No 726/2004

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This notification is a referral under Article 20 of Regulation (EC) No 726/2004 to the PRAC made by the European Commission (EC):

Product(s) Name(s)	Lemtrada
Active substance(s)	Alemtuzumab
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Sanofi Belgium

Alemtuzumab (Lemtrada) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) to slow the accumulation of physical disability and reduce the frequency of clinical exacerbations.

The mechanism by which alemtuzumab exerts its therapeutic effects in RRMS is unknown but may involve immunomodulation through the depletion and repopulation of lymphocytes. Alemtuzumab binds to CD52[1], a cell surface antigen present at high levels on T and B lymphocytes[2], and at lower levels on natural killer cells, monocytes, and macrophages. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

During the assessment procedure 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, was

[1] CD52 - cluster of differentiation 52

[2] T cells (thymus cells) and B cells (bone marrow cells)

available on these concerns during the PSUSA assessment, precluding a thorough evaluation.

Due to the seriousness of the adverse events and the time constraints within the PSUSA procedure to obtain further information related to these issues, the safety aspects mentioned above could not be satisfactorily investigated and addressed. Although efficacy of alemtuzumab in RRMS patients is well established, the risks can impact the benefit-risk balance of the medicinal product Lemtrada. Therefore, the impact of the new information on these safety concerns on the benefit-risk balance of Lemtrada, taking into account the current target population, needs to be further assessed.

An in-depth review of the benefit-risk balance of Lemtrada in the approved indication in the EU is needed, including whether any further risk minimisation or other measures should be implemented. Within this review, the views from clinical experts may need to be sought.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above safety concerns and their impact on the benefit-risk balance for the centrally authorised medicinal product Lemtrada (alemtuzumab).

The EC requests the Agency to give its opinion as soon as on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked. The Agency is invited to consider whether their opinion can be given by 31 October 2019.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Due to the seriousness of the adverse events, the EC requests the Agency to give its opinion, as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of this medicinal product.

[redacted]

Signed Date 10.04.2019

Olga Solomon
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Health and Food Safety Directorate General