12th April 2019

Alemtuzumab (LEMTRADA): Restriction of use due to serious safety concerns

Dear Healthcare Professional,

Sanofi in agreement with the European Medicines Agency (EMA) and the Medicines Authority would like to inform you of the following:

EMA is reviewing the benefits and risks of Lemtrada (alemtuzumab) for the treatment of multiple sclerosis following reports of serious cardiovascular reactions, newly identified autoimmune hepatitis and haemophagocytic lymphohistiocytosis. The following measures have been agreed until this review is finalised.

Summary

- Treatment of new patients should only be initiated in adults with highly active relapsing remitting multiple sclerosis (RRMS), despite a full and adequate course of treatment with at least two other disease modifying treatments (DMTs), or in adult patients with highly active RRMS where all other DMTs are contraindicated or otherwise unsuitable.

- Patients receiving treatment with alemtuzumab should have vital signs monitored, including blood pressure measures, before and periodically during alemtuzumab infusion. If clinically significant changes in vital functions are observed, discontinuation of infusion and additional monitoring, including ECG, should be considered.

- Liver function should be evaluated before and during treatment.

- In case of symptoms of hepatic injury, or other serious immune mediated reactions, treatment should only be re-administered following careful consideration.

- Patients should be advised to immediately seek medical help if they experience symptoms occurring some days after the infusion or symptoms of hepatic injury.

Background information

On 11 April 2019, EMA has started a review of the benefit-risk balance of Lemtrada in the approved indication. This is due to new findings of serious safety concerns from post-marketing use, including fatal cases, cardiovascular adverse events in close temporal association with Lemtrada infusions, and immune-mediated adverse reactions. There are currently serious questions as to whether the current risk minimization measures are sufficient to adequately manage these risks.

During this review, treatment in new patients should only be initiated in adult patients with highly active relapsing remitting multiple sclerosis (RRMS), despite a full and adequate course of treatment with at least two other disease modifying treatments (DMTs), or in adult patients

with highly active RRMS where all other DMTs are contraindicated or otherwise unsuitable.

Patients being treated with Lemtrada who are benefitting from it may continue treatment in consultation with their prescriber.

In light of these emerging post-marketing data, alemtuzumab is suspected to be related to the following:

Autoimmune hepatitis and hepatic injury

Cases of hepatic injury including elevations of serum transaminases and autoimmune hepatitis (including fatal cases) have been reported in patients treated with alemtuzumab. Before and during the treatment liver function should be evaluated. Patients should be informed about the risk of hepatic injury and related symptoms. In case of these symptoms, treatment should only be re-administered following careful consideration.

Other serious reactions temporally associated with alemtuzumab infusion

During post-marketing use, cases of pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke) and cervicocephalic (e.g. vertebral, carotid) arterial dissection have been reported. Reactions may occur following any of the doses during the treatment course. In the majority of cases, time to onset was within 1-3 days of LEMTRADA infusion. Patients should be informed about the signs and symptoms, and advised to seek immediate medical attention if any of these symptoms occur.

Vital signs, including blood pressure measures, should be monitored before and periodically during LEMTRADA infusion. If clinically significant changes in vital functions are observed, discontinuation of infusion and additional monitoring, including ECG, should be considered.

Haemophagocytic lymphohistiocytosis (HLH)

During post-marketing use, HLH has been reported in patients treated with LEMTRADA. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Symptoms have been reported to occur within a few months to four years following the initiation of treatment. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

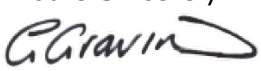
Call for reporting

Healthcare professionals are encouraged to report adverse events in patients treated with Lemtrada to Medicines Authority Post-licensing Directorate, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 Malta, MALTA, or at: www.medicinesauthority/adrportal

Company contact point

If you have any questions or require additional information, please call Sanofi Malta Ltd, Level 2, Fort Business Centre, Mriehel Bypass, B'Kara BKR3000, Malta – Tel: 21 493 022

Yours Sincerely



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