January 2020

Direct Healthcare Professional Communication

LEMTRADA ▼ (alemtuzumab): Restricted indication, additional contraindications and risk minimisation measures

Dear Healthcare Professional,

This letter is sent in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) to inform you of the following:

Summary

Lemtrada is associated with the risk of serious, sometimes fatal adverse reactions. New restrictions on its use have been introduced to replace previous interim measures as follows:

Lemtrada is 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 or**
- **Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in 1 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.**

Additional contraindications:

  - **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 anti-platelet or on anti-coagulant therapy**
  - **concomitant autoimmune diseases other than multiple sclerosis**

- **Lemtrada should only be administered in a hospital setting with ready access to intensive care, since serious reactions such as myocardial ischaemia or infarction, cerebral haemorrhage or pulmonary haemorrhage can occur during or shortly after the infusion. Patients should be carefully monitored, and be advised to contact their doctor if any signs or symptoms of serious reactions occur shortly after the infusion.**
- **Patients should be monitored for autoimmune disorders for at least 48 months after the last infusion and be advised that these disorders may also occur more than 48 months after the last infusion.**

Background information

EMA has reviewed the benefit-risk balance of Lemtrada in light of new findings of serious, sometimes fatal adverse reactions reported during postmarketing use. The existing risk minimisation measures were not adequate for managing these risks.

EMA has concluded that myocardial ischaemia, myocardial infarction, cerebral haemorrhage, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage and thrombocytopenia may infrequently occur in close temporal association with the Lemtrada infusion. In many cases, onset of the reactions was within a few days after the infusion and the patients had no classical risk factors for the events.

Lemtrada is also causally linked with autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH). HLH is a life-threatening syndrome of immune activation characterised by fever, hepatomegaly and cytopenia. It is associated with high mortality if not recognised early and treated.

Autoimmune disorders occur within months to years following the initiation of Lemtrada treatment. Clinical examination and laboratory tests should be conducted periodically until at least 48 months after the last course of Lemtrada to monitor for early signs of autoimmune diseases. Patients who develop autoimmunity should be evaluated for other autoimmune-mediated conditions. Patients and physicians should be aware of the potential for autoimmune disorders occurring more than 48 months after the last Lemtrada treatment.

It has also been noted that Epstein-Barr virus (EBV) reactivation, including cases of severe EBV hepatitis, has been reported in Lemtrada-treated patients.

EMA's review concluded on a need to restrict Lemtrada's therapeutic indication (see Summary above), and introduce new contraindications (see Summary above) and risk minimisation measures.

Lemtrada treatment should be initiated and supervised only by a neurologist experienced in the treatment of patients with multiple sclerosis and it should be given only in a specialised hospital setting with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia, cerebrovascular adverse reactions, autoimmune conditions and infections, should be available.

The following infusion instructions are intended to reduce serious reactions temporally associated with Lemtrada infusion

- Pre-infusion evaluations:
    - Obtain a baseline ECG and vital signs, including heart rate and blood pressure measurements.
    - Perform laboratory tests (full blood count with differential white cell count, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy).
- During infusion:
    - Perform continuous/frequent (at least every hour) monitoring of heart rate, blood pressure and overall clinical status of the patients
    - Discontinue the infusion
        - In case of a severe adverse event
        - If the patient shows clinical symptoms suggesting development of a serious adverse event associated with the infusion (myocardial ischaemia, haemorrhagic stroke, cervicocephalic arterial dissection or pulmonary alveolar haemorrhage)

- Post-infusion:
    - Observation for infusion reactions is recommended for a minimum of 2 hours after Lemtrada infusion. Patients with clinical symptoms suggesting development of a serious adverse event temporally associated with the infusion (myocardial ischaemia, haemorrhagic stroke, cervicocephalic arterial dissection and pulmonary alveolar haemorrhage) should be closely monitored until complete resolution of the symptoms. The observation time should be extended (hospitalisation) as appropriate. The patients should be educated on the potential for delayed onset of infusion-associated reactions and instructed to report symptoms and seek appropriate medical care.
    - Platelet counts should be obtained immediately after infusion on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Clinically significant thrombocytopenia needs to be followed until resolution. Consider referral to a haematologist for management.

The product information is being updated to include these measures. The physician's guide and patient card will also be updated.

Call for reporting

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It is easiest and quickest to report suspected adverse reactions online via the Yellow Card website - https://www.gov.uk/yellowcard/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary), by emailing yellowcard@mhra.gov.uk, at the back of the British National Formulary (BNF), by telephoning the Commission on Human Medicines (CHM) free phone line: 0800 731 6789, or by downloading and printing a form from the Yellow Card section of the MHRA website.

Suspected adverse reactions should also be reported to Sanofi. Tel: 0800 0902314. Email: UK-drugsafety@sanofi.com

Further Information:
If you require any further information, please contact Sanofi Medical Information department. Telephone: 0845 372 7101 or email UK-medicalinformation@sanofi.com

Yours Sincerely

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