Novartis Ireland Limited
Beech House
Beech Hill Office Campus
Clonskeagh, Dublin 4.

NOVARTIS

5th November 2013

Direct Healthcare Professional Communication

Haemophagocytic syndrome reported in patients treated with fingolimod (Gilenya)

Dear Healthcare Professional,

The Irish Medicines Board in accordance with the European Medicines Agency and Novartis would like to inform you on the reporting of 2 fatal cases of hemophagocytic syndrome in MS patients treated with fingolimod.

Summary

- Two fatal cases of haemophagocytic syndrome (HPS), both in the context of an infection have been reported in patients treated with fingolimod 0.5 mg/day for 9 and 15 months, respectively.

- An early diagnosis of HPS is important in order to improve the prognosis by early initiation of treatment of the HPS and/or the underlying condition, e.g. a viral infection

- Symptoms and signs often associated with HPS are:

    - fever, asthenia, hepato-splenomegaly and adenopathy which may be associated with more severe manifestations such as hepatic failure or respiratory distress.

    - progressive cytopenia, markedly elevated serum ferritin levels, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, hepatic cytolysis and hyponatremia.

Further information on haemophagocytic syndrome and the recommendations

The present letter aims to raise the awareness of the healthcare professionals regarding the difficulty to diagnose HPS and the importance of an early diagnosis as there is a risk of a worse outcome when the diagnosis and thus the treatment are delayed.

HPS is a very rare and potentially life-threatening hyper-inflammatory syndrome, that has been described in association with infections (primary or reactivation of virus infections e.g. Epstein Barr Virus), malignancies (e.g. lymphoma), immune deficiency and a variety of autoimmune diseases (e.g. lupus).
It should be noted that Gilenya is a selective immunosuppressant and its effect on the immune system increases the risk of infections. Cases of severe infections have been reported during its use. The Summary of Product Characteristics (SmPC) of Gilenya has been updated to mention that fatal cases of HPS have been reported.
Diagnosis

Clinically, HPS often manifests with fever, asthenia, hepato-splenomegaly and adenopathy which may be associated with more severe manifestations such as hepatic failure or respiratory distress. The outcome of HPS can be fatal, especially when an appropriate diagnosis and treatment are delayed.

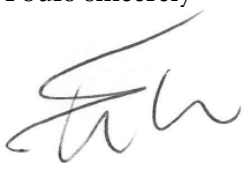
Laboratory findings often consist of progressive cytopenia, markedly elevated serum ferritin levels, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, hepatic cytolysis and hyponatremia.
The cytopathological feature of HPS is the activation of well differentiated macrophages with prominent hemophagocytosis in hematopoietic organs or lymph nodes.
Diagnosis requires the assessment of all clinical and laboratory findings and should be confirmed by a specialist.
Treatment
Early recognition and prompt treatment have been shown to improve prognosis of HPS. There is no defined standard treatment for HPS to date; diverse chemotherapeutic agents have been described to improve the outcome in some situations. In addition to treatment of the syndrome, it is also important to treat the underlying condition (e.g. viral infection).

Call for reporting
Healthcare professionals should report any suspected adverse reactions associated with use of Gilenya in accordance with the national requirements via the national spontaneous reporting system accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option. **FREEPOST,** Pharmacovigilance Section, Earlsfort Centre, Earlsfort Terrace, Dublin 2.
Healthcare professionals may also report any suspected adverse reactions associated with use of Gilenya to Novartis Ireland Limited, Beech House, Beech Hill Office Campus, Clonskeagh, Dublin 4.Tel: 01-2601255, Fax: 01-2838777

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

Should you require any further information please contact Novartis Ireland Limited, Beech House, Beech Hill Office Campus, Clonskeagh, Dublin 4.Tel: 01-2601255, Fax: 01-2601263

Yours sincerely



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Dr. Eva Lindgren
Medical Director
Novartis Ireland Ltd