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Direct Healthcare Professional Communication

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Gilenya (fingolimod) – Updated recommendations to minimise the risk of drug-induced liver injury (DILI)

Dear Healthcare Professional,
In agreement with European Medicines Agency (EMA) and Health Product Regulatory Authority (HPRA), Novartis would like to inform you of important updated information to help minimise the risk of DILI in patients treated with Gilenya.

Summary

- **Cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported in patients treated with fingolimod.**
- **The guidance for monitoring liver function and the criteria for discontinuation have been updated with additional details to minimise the risk of DILI:**
  - **Liver function tests including serum bilirubin should be performed before starting treatment and at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after fingolimod discontinuation.**
  - **In the absence of clinical symptoms, if liver transaminases are:**
    - **greater than 3 times the upper limit of normal (ULN) but less than 5 times ULN without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) should be instituted.**
    - **at least 5 times ULN or at least 3 times ULN associated with any increase in serum bilirubin, fingolimod should be discontinued. If serum levels return to normal, fingolimod may be restarted based on a careful benefit-risk assessment of the patient.**
  - **In the presence of clinical symptoms suggestive of hepatic dysfunction:**
    - **Liver enzymes and bilirubin should be checked promptly and fingolimod should be discontinued if significant liver injury is confirmed.**

Background

Gilenya is indicated as disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for adults and children aged 10 years and older:
-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 2 or more disabling relapses in one 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.

Following the most recent periodic review of safety data, three cases of liver failure requiring liver transplant have been reported in patients treated with fingolimod, including one case implying a strong causal relationship with the product. Cases of clinically significant liver injury have also been reported. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose and have also been reported after prolonged use.

During clinical development, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of adult patients treated with fingolimod 0.5 mg and elevations 5-fold the ULN occurred in 1.8% of patients on fingolimod. Fingolimod was discontinued if the elevation exceeded 5 times the ULN, recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod.

Hepatic enzyme increase is a very common adverse drug reaction of the product but due to the seriousness and the severity of recent reported cases, recommendations for discontinuation of the therapy and monitoring have been strengthed and clarified to minimize the risk of DILI. Bilirubin should be checked together with liver transaminase enzymes and liver function tests should be performed regularly until 2 months after fingolimod discontinuation. In case of symptoms suggestive of hepatic dysfunction, fingolimod should be discontinued if significant liver injury is confirmed and treatment should not be resumed unless a plausible alternative aetiology for the signs and symptoms of liver injury can be established.

The product information and the educational materials for Gilenya, including the checklist for prescribers will be updated to reflect these new recommendations.

Call for reporting

▼ Gilenya is subject to additional monitoring. Reporting suspected adverse reactions of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported via HPRA Pharmacovigilance, website: www.hpra.ie; email medsafety@hpra.ie; Tel +353 1 6764971; or Fax +353 1 6762517.
Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.

Company contact point

If you have any further queries please contact bishember.kathuria@novartis.com or at 01 260 1255.

Yours Sincerely,

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