NOVARTIS

10 November 2020

Direct Healthcare Professional Communication:
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 Medicines and Healthcare products Regulatory Agency (MHRA), 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) measurement 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.

In clinical trials, 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.

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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 strengthened and clarified to minimize the risk of DILI. Liver function tests, including transaminases and bilirubin, should be checked regularly until 2 months after discontinuation of fingolimod. 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

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Card website - www.mhra.gov.uk/yellowcard or via the Yellow Card app available from the Apple App Store or Google Play 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
- by downloading and printing a form from the Yellow Card website (see link above)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, investigation results, treatment dates, and product brand name.

Gilenya▼ is subject to additional monitoring. This will allow quick identification of new safety information.
Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com.

Further copies of this letter can be obtained via the electronic medicines compendium (eMC) website by visiting https://www.medicines.org.uk/emc.

Company contact point

If you have any questions or require further information, please contact Novartis Medical Information department on 01276 698370 or email medinfo.uk@novartis.com.

Yours faithfully,

Dr. Dina Christopoulou
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