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 <National Competent Authority>, 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 increased 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 strengthen and clarify to minimize the risk of DILI. Bilirubin should be checked together with liver transaminase enzymes and liver tests function should be performed regularly until 2 months after fingolimod discontinuation. In case of symptoms suggestive 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 report any suspected adverse reactions associated with the use of fingolimod in accordance with the national requirements via the national spontaneous reporting system, to:

<Details of national reporting systems as per Appendix V to be included prior to submission to national MS Competent Authorities>

▼ Gilenya is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Gilenya (fingolimod 0.25 mg and 0.5 mg capsules)
Marketing authorisation holder(s)	Novartis Europharm Limited
Safety concern and purpose of the communication	Updated recommendations to minimise the risk of drug-induced liver injury (DILI)
DHPC recipients	Neurologists, pediatric neurologists, general practitioners, specialists in Hepatology and Gastroenterology, professional societies in neurology and in hepatology/gastroenterology, pharmacies, hospital pharmacist and other recipients to be agreed with the National Competent Authorities (NCAs). Details for each country to be discussed and agreed with the National Competent Authorities.
Member States where the DHPC will be distributed	The communication will be disseminated in all EU Member States where Gilenya is marketed, as well as Iceland, Liechtenstein and Norway.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	**01 October 2020**
DHPC and communication plan (in English) agreed by CHMP	**15 October 2020**
Submission of translated DHPCs to the national competent authorities for review	**22 October 2020**
Agreement of translations by national competent authorities	**29 October 2020**
Dissemination of DHPC	**10 November 2020**