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Cardiovascular Adverse Events after the First Dose of Gilenya®

Dear Healthcare Professional

Novartis Saudi Arabia, in collaboration with Saudi Food and Drug Authority (SFDA), would like to inform you about the update to the Prescribing Information for Gilenya (fingolimod). GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The changes to the Prescribing Information include: revised recommendation for monitoring after first dose of Gilenya, new contraindication section; and revised recommendations for the use of Gilenya in patients with pre-existing cardiovascular conditions who may not tolerate Gilenya-induced bradycardia and concomitant use with medications that affect the heart rate or atrioventricular (AV) conduction.

Please review the new recommendations, which are summarized below, before prescribing Gilenya.

Recommendations for First Dose Monitoring

- Initiation of GILENYA treatment results in a decrease in heart rate. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients
- The first dose of GILENYA should be administered in a setting in which resources are available to appropriately manage symptomatic bradycardia
- In order to assess the patient's response to the first dose of GILENYA, all patients should be observed for a period of at least 6 hours after the first dose of GILENYA to monitor for signs and symptoms of bradycardia. Additionally,
  - An ECG should be performed prior to dosing GILENYA
  - Blood pressure and pulse should be monitored hourly
  - An ECG should be performed at the end of the observation period
- Additional observation beyond 6 hours should be instituted until the finding has resolved in the following situations:
  - The heart rate 6 hours post-dose is <45 beats per minute (bpm)
  - The heart rate 6 hours post-dose is the lowest value observed post-dose
  - The ECG 6 hours post-dose shows new-onset second-degree or higher AV block
- Should post-dose symptomatic bradycardia occur:
  - Initiate appropriate management
  - Begin continuous ECG monitoring

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- Continue observation until the symptoms resolve
- Should a patient require pharmacologic intervention for symptomatic bradycardia:
- Continuous overnight ECG monitoring in a medical facility should be instituted
- First dose monitoring strategy should be repeated after the second dose of GILENYA

Contraindications to the Use of GILENYA

GILENYA is contraindicated in patients with:

- Recent (within the last 6 months) myocardial infarction (MI), unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- History or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block or sick-sinus syndrome, unless the patient has a functioning pacemaker
- Baseline QTc interval $\geq$ 500 ms
- Treatment with Class 1a or Class III anti-arrhythmic drugs

Recommendations for Use of GILENYA in Patients with Pre-Existing Cardiovascular Conditions

- Patients with some pre-existing conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, and sino-atrial heart block) may poorly tolerate the GILENYA-induced bradycardia, or experience serious rhythm disturbances after the first dose of GILENYA.
- Prior to treatment with GILENYA, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with GILENYA, should be monitored overnight with continuous ECG in a medical facility after the first dose
- Since initiation of GILENYA treatment results in decreased heart rate and may prolong the QT interval, overnight continuous ECG monitoring is recommended in patients who:
  - have prolonged QTc interval before or during the 6 hour observation (>450 ms males,
  - >470 ms females)
  - are at higher risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome)
  - are on concurrent therapy with drugs that prolong the QT interval and have a known risk of torsades de pointes. Please refer to the list titled "Drugs with a Risk of Torsades de Pointes" at www.qtdrugs.org

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Recommendations for Use of GILENYA with Concomitant Medications That Slow Heart Rate or AV Conduction

- Because the initiation of GILENYA treatment is also associated with slowing of the heart rate, concomitant use of these drugs during GILENYA initiation may be associated with severe bradycardia or heart block
- The possibility to switch to drugs that do not slow the heart rate or AV conduction should be evaluated by the physician prescribing these drugs before initiating GILENYA. In patients who cannot switch, overnight continuous ECG monitoring is recommended after the first dose

This letter does not review all the updates to the GILENYA Prescribing Information. For additional updates, including those related to re-initiation of GILENYA therapy following discontinuation, see the full Prescribing Information. Please note that this presentation of the risk profile for GILENYA is not comprehensive. Please refer to the full Prescribing Information for a complete discussion of the risks associated with GILENYA.

The content of this letter has been agreed with the Saudi Food & Drug Authority.

To report adverse events potentially associated with GILENYA, please call Novartis Saudi Arabia (01 4658882) Or send it to the national Pharmacovigilance and Drug Safety Center at Fax: +966-1-2057662 or by email to: npc.drug@sfda.gov.sa

Yours sincerely

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