Sphingolin (Fingolimod) Prescriber Checklist

Important points to remember before, during and after treatment-Summary of Recommendations

This document is approved by the Executive Directorate of Pharmacovigilance at SFDA

Considerations in Sphingolin (Fingolimod) Patient Selection

Sphingolin (Fingolimod) is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS) for the following groups of adult patients. While many patients are suitable for treatment, the following section highlights patients in whom Sphingolin (Fingolimod) is contraindicated or not recommended.

Sphingolin (Fingolimod) causes transient heart rate reduction and may cause atrioventricular (AV) conduction delays following initiation of treatment. All patients should be monitored for a minimum of 6 hours on treatment initiation. Below is a brief overview of monitoring requirements.

Sphingolin (Fingolimod) is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis.

Contraindications:

Sphingolin (Fingolimod) is contraindicated in patients with:

• Hypersensitivity to Sphingolin (Fingolimod) hydrochloride or to any of the excipients in the formulation of (Sphingolin (Fingolimod)) or component of the container

• Increased risk for opportunistic infections, including those who are immunocompromised due to treatment (e.g. antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g. immunodeficiency syndrome)

• Severe active infections, including active chronic bacterial, fungal or viral infections (e.g. hepatitis, tuberculosis)

• Known active malignancies (except patients with basal cell carcinoma (BCC)

• In the previous 6 months, myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NVHA) class III/IV heart failure.

The following patients should not be treated with Sphingolin (Fingolimod)

• Those who are pregnant or breast feeding

• Those who are taking Class Ia or Class III antiarrhythmics

• Pediatric patients

Should not be used Consider Sphingolin (Fingolimod) only after performing risk/benefit analysis and consulting a cardiologist
Consult cardiologist regarding appropriate first-dose monitoring

History of bradyarrhythmia † , QTc prolongation > 470 msec (females) or > 450 msec (males), or risk factors for QT prolongation, severe sleep apnoea, significant cardiovascular disease ‡, uncontrolled hypertension, cerebrovascular disease, history of recurrent syncope	At least overnight extended monitoring is recommended

Consult cardiologist regarding possibility of switching to non-heart-rate-lowering drugs	
Taking beta-blockers, heart-rate-lowering Calcium channel blockers, or other substances That are known to lower the heart rate	If change in medication is not possible Extend monitoring to at least overnight

† Bradyarrhythmia includes the following: second-degree Mobitz type II or higher atrioventricular (AV) block, sick sinus syndrome, sinoatrial heart block, history of symptomatic bradycardia.

‡ Significant cardiovascular diseases includes the following: ischaemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest.

§ Such as verapamil or diltiazem

|| Includes digoxin, cholinesterase inhibitors, or pilocarpine.

Physician's checklist- Recommended Steps to Managing Patients on fingolimod
Patient's name: …… Date of birth: ……

	Prior to initiating treatment
☐	Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines
☐	Conduct baseline electrocardiogram (ECG) and blood pressure measurement
☐	Treatment with Sphingolin (Fingolimod) should not be used in the following patients, unless anticipated benefits outweigh the potential risks • Those with bradyarrhythmia, significant cardiovascular disease, significant QT-interval prolongation, uncontrolled hypertension, cerebrovascular disease, severe untreated sleep apnoea, or a history of recurrent syncope Seek advice from a cardiologist regarding the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended] • Those receiving concurrent therapy with beta-blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g., digoxin, cholinesterase inhibitors, or pilocarpine) Seek advice from a cardiologist regarding a switch to non-heart-lowering medicinal products prior to initiation of treatment. If heart-rate- lowering cannot be stopped, seek advice from cardiologist regarding the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended
☐	Avoid co-administration of anti-neoplastic, immunosuppressive or immunomodulatory therapies due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration
☐	Obtain recent (within 6 months) transaminase, and bilirubin levels
☐	Obtain recent (within 6 months or after discontinuation of prior therapy) peripheral lymphocyte count (complete blood count (CBC). Treatment should not be initiated when lymphocyte counts are consistently below normal range.
☐	Confirm a negative pregnancy test result in women of childbearing potential
☐	Counsel on the need for effective contraception in women of childbearing age up to at least 2 months after completion or discontinuation of treatment, due to teratogenic risk to fetus.
☐	Delay initiation of treatment in patients with severe active infection until resolved
☐	Check varicella zoster virus (VZV) antibody status in patients without a healthcare-professional-confirmed history of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for 1 month to allow full affect of vaccination to occur
☐	Conduct an ophthalmologic evaluation in patients with history of uveitis or diabetes mellitus
☐	Conduct a dermatologic examination. The patient should be referred to a dermatologist if suspicious lesions, potentially indicative of basal cell carcinoma, are detected
☐	Provide patients with a Patient Reminder Card

Physician's checklist- Recommended Steps to Managing Patients on fingolimod
Patient's name: …… Date of birth: ……

¶ Bradyarrhythmia includes the following: second-degree Mobitz type II or higher AV block, sick sinus syndrome, sinoatrial heart block, history of symptomatic bradycardia.

Significant cardiovascular disease includes the following: ischaemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest.

	First-dose monitoring up to 6 hours post-dose and beyond, as necessary
☐	Perform ECG and blood pressure 6 hours after the first dose
☐	Monitor for signs and symptoms of bradyarrhythmia with hourly pulse and blood pressure measurements at least up to 6 hours post-dose. Initiate continuous monitoring as required.
☐	Extend monitoring if: • Heart rate at 6 hours is < 45 bpm or is lowest post-dose value • Heart rate 6 at hours shows new onset second degree or higher AV block • If ECG at 6 hours shows QTC >500 msec. (overnight monitoring required)
☐	Counsel patients that their ability to drive and use machines may be affected during and potentially after this period.

Physician's checklist- Recommended Steps to Managing Patients on fingolimod
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	During Treatment
☐	Conduct a full ophthalmologic evaluation in all patients at 3 to 4 months after starting treatment and in any patient complaining of visual disturbances >> Conduct periodic ophthalmologic evaluations in patients with history of uveitis or diabetes mellitus >> Counsel patients to report any visual disturbance during treatment >> Evaluate the fundus, including the macula, and discontinue treatment if macular oedema is confirmed Counsel patients to report signs and symptoms of infection >> Prompt antimicrobial treatment should be initiated if indicated >> Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with cryptococcal meningitis, and initiate appropriate treatment if diagnosed (cryptococcal meningitis sometimes fatal, 2-3 years after treatment >> Suggestive of progressive multifocal leukoencephalopathy (PML). If PML is suspected, treatment with Sphingolin (Fingolimod) should be suspended until PML has been excluded (cases of PML 2-3 years after treatment) >> If a patient develops a serious infection, treatment should be suspended >> Discontinue treatment in disseminated herpetic infections.
☐	Peripheral lymphocyte count (CBC) should be monitored during treatment, at month 3 and at least yearly thereafter. Treatment should be interrupted if lymphocyte count is confirmed as <0.2x109 L. The approved dosing of 0.5 mg once daily when restarting Sphingolin (Fingolimod) should be administered. Other dosing regimens Be vigilant for clinical symptoms or MRI findings that may be suitable
☐	Check liver transaminases and serum bilirubin before starting treatment and at months 1, 3, 6, 9, and 12 and periodically thereafter, until 2 months after Sphingolin (Fingolimod) discontinuation, or at any time there are signs or symp- toms of hepatic dysfunction 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, fingoli- mod should be discontinued. If serum levels return to normal, Sphingolin (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 Sphingolin (Fingolimod) should be discontinued if significant liver injury is confirmed.
☐	During treatment and for up to 2 months after discontinuation >> Vaccinations may be less effective >> Live attenuated vaccines may carry a risk of infection and should be avoided
☐	Counsel patient to advise physician immediately if she becomes pregnant Pregnancy tests should be repeated at suitable intervals. Discontinue treatment if a patient becomes pregnant To help determine the effects of Sphingolin (Fingolimod) exposure in pregnant women with MS, physicians are encouraged to report any pregnancy outcomes

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☐	Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended, with skin examination prior to treatment initiation and then yearly taking into consideration clinical judgment and referral to a dermatologist if suspicious lesions, potentially indicative of basal cell carcinoma or other cutaneous neoplasms, are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA -photochemotherapy.

After treatment discontinuation	
☐	Repeat first-dose monitoring as for treatment initiation when treatment is interrupted for: >> One day or more during the first 2 weeks of treatment >> More than 7 days during week 3 and 4 of treatment >> More than 2 weeks after 1 month of treatment
☐	Counsel patients to report signs and symptoms of infection for up to 2 months after discontinuation.
☐	Counsel patients that effective contraception is needed for 2 months after discontinuation

Treatment initiation algorithm

All patients will need to be monitored for at least 6 hours during treatment initiation, as described in the algorithm below. In addition, for patients in whom Sphingolin (Fingolimod) is not recommended, advice should be sought from a cardiologist regarding appropriate monitoring; at least overnight monitoring is recommended for this group.

Treatment initiation algorithm

Monitor for a minimum of 6 hours

- Perform ECG and BP measurement
- Monitor for a minimum of 6 hours for signs and symptoms of bradycardia, with hourly pulse and BP checks. If patient is symptomatic, continue monitoring until resolution
  - Continuous (real-time) ECG is recommended throughout the 6-hour period
- Perform ECG at 6 hours

- Did the patient require pharmacologic intervention at any time during the monitoring period?

Yes → Monitor overnight.

First-dose monitoring should be repeated after the second dose of fingolimod

No

- Did third-degree AV block occur at any time during the monitoring period?

Yes → Extent monitoring at least overnight, until the findings have resolved

No

At the end of the monitoring period, have any of the following criteria been met?

- HR < 45 bpm
- ECG shows new-onset second-degree or Higher AV block or QTc interval ≥ 500 msec

Yes →

No

- At the end of the monitoring period, is the HR the lowest since the first dose was administered?

Yes → Extend monitoring for at least 2 hours and until heart rate increases

No

First-dose monitoring is complete

The above first-dose monitoring procedure should also be followed at reinitiation of treatment if fingolimod therapy is discontinued for

- One day or longer within the first 2 weeks of treatment
- More than 7 days during weeks 3 and 4 of treatment
- More than 2 weeks after the first month of treatment

BP= blood pressure; ECG=electrocardiogram;

HR= heart rate; QTc= heart-rate-corrected QT interval

Reporting adverse events:

Healthcare professionals should report any suspected adverse Therefore, if you receive or observe any adverse reaction you can reach the following contacts:

National Pharmacovigilance & Drug Safety Centre at Saudi Food and Drug Authority (SFDA):
SFDA call centre: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Marketing Authorization Holder Contact Information:
Saudi Amarox Industrial Company
Ms. Razan almalki
Pharmacovigilance Specialist
Al Jamiyah Street – Al Malaz – Riyadh Code 12629, Saudi Arabia.
Phone: +966 11 226 8850

Mobile: +966 531215235

Email: r.almalki@amaroxpharma.com