hikma.

Gemorya

Prescriber Checklist

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

Version 3, October 2021

Considerations in fingolimod patient selection

Fingolimod is suitable for adult and paediatric patients (≥10 years old) for the treatment of highly active relapsing remitting MS (RRMS)*. While many patients may be suitable for treatment, the following section highlights patients in whom Fingolimod is contraindicated or not recommended.

Considerations for treatment initiation

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. Refer to page 4 for more information.

Contraindications

Known immunodeficiency syndrome, patients with increased risk for opportunistic infections (including immunocompromised patients), severe active infections, active chronic infections, known active malignancies, severe liver impairment, severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs, patients with second-degree Mobitz type II AV block or third-degree AV block, or sick-sinus syndrome (if they do not wear a pacemaker), patients with a baseline QTc interval of ≥500 msec, patients who in the previous 6 months had myocardial infarction, unstable angina, stroke/transient ischaemic attack, decompensated heart failure, or New York Heart Association class III/IV heart failure, pregnant women, women who are breast-feeding, women of child-bearing potential (WOCBP; including adolescents) not using effective contraception, and patients with hypersensitivity to the active substance or to any of the excipients.

Not recommended Consider only after performing risk/benefit analysis and consulting a cardiologist	
Sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT-interval prolongation†, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea	□ **At least overnight extended monitoring is recommended** □ **Consult cardiologist regarding appropriate first-dose monitoring**
Taking beta-blockers, heart-rate-lowering calcium channel blockers‡, or other substances that are known to lower the heart rate§	□ **Consult cardiologist regarding possibility of switching to non-heart-rate-lowering drugs** □ **If change in medication is not possible, extend monitoring to at least overnight**

*Fingolimod is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients 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.

†QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males).

‡Includes verapamil or diltiazem.

§Includes ivabradine, digoxin, anticholinesterases, or pilocarpine.

Recommended steps to managing patients on Fingolimod

The checklist and schematic that follow are intended to assist in the management of patients on Fingolimod. Key steps and considerations while starting, continuing, or discontinuing treatment are provided.

Patient's name: .....

Date of birth: .....

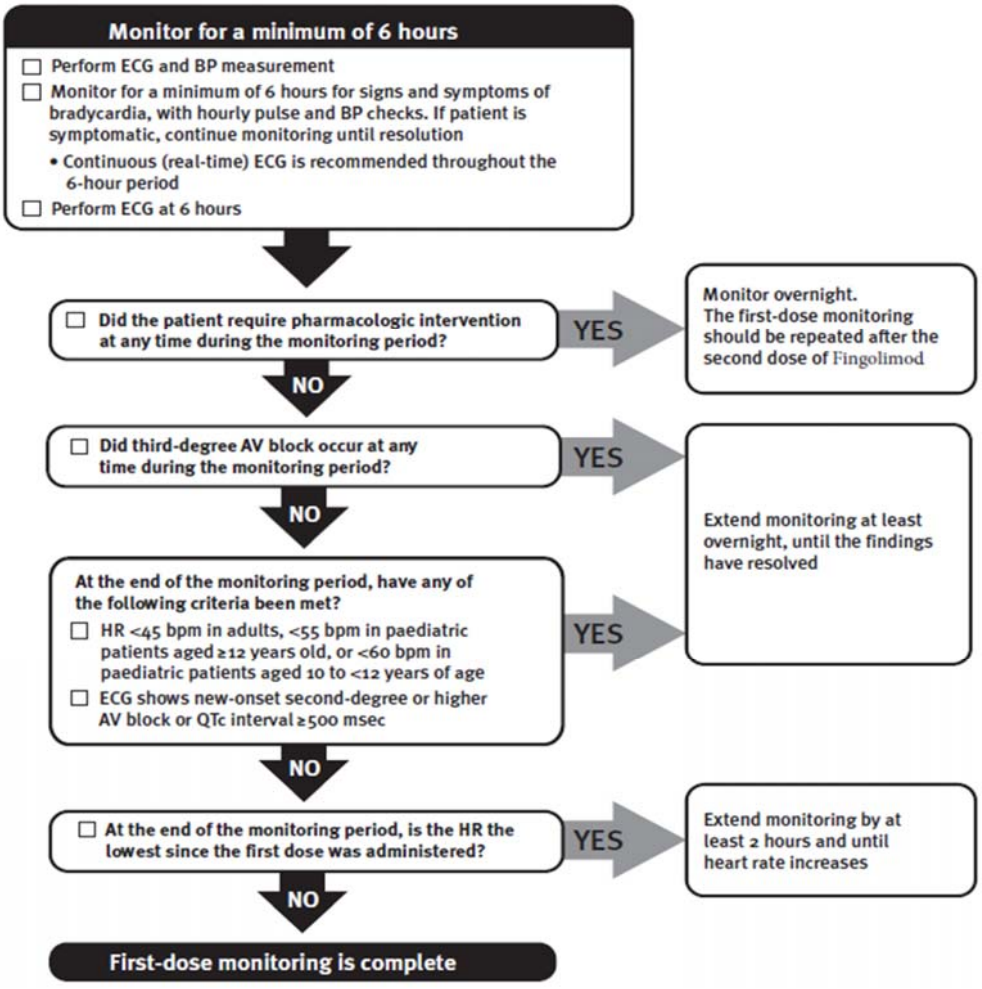
Consultant: .....

Hospital number: .....

	Prior to initiating treatment
☐	Treatment with Fingolimod is not recommended in the following patients, unless anticipated benefits outweigh the potential risks: Those with sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT-interval prolongation*, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea ☐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 (e.g. verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents, or pilocarpine) ☐Seek advice from a cardiologist regarding a switch to non-heart-rate-lowering medicinal products prior to initiation of treatment ☐If heart-rate-lowering medication cannot be stopped, seek advice from a cardiologist regarding the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended *QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males).
☐	For paediatric patients, assess Tanner staging, measure height and weight, and consider a complete vaccination schedule, as per standard of care
☐	Ensure Patients are not concomitantly taking Class Ia or Class III anti-arrhythmic medicines
☐	Conduct baseline electrocardiogram (ECG) and blood pressure (BP) measurement
☐	Avoid co-administration of anti-neoplastic, immunomodulatory or immunosuppressive 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) full blood count
☐	Inform WOCBP (including adolescents and their parents/caregivers) that Fingolimod is contraindicated in pregnant women and WOCBP not using effective contraception

☐	Fingolimod is teratogenic. Confirm a negative pregnancy test result in WOCBP (including adolescents) prior to starting treatment and repeat at suitable intervals during treatment
☐	Inform WOCBP (including adolescents and their parents/caregivers) about the serious risks of Fingolimod to the foetus
☐	Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card
☐	Counsel WOCBP (including adolescents and their parents/caregivers) to avoid pregnancy and use effective contraception both during treatment and for 2 months after treatment discontinuation. Counselling should be facilitated by the Pregnancy-Specific Patient Reminder Card
☐	Delay initiation of treatment in patients with severe infection until resolved
☐	Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post- marketing setting. Cancer screening (including a Pap test), and vaccination for HPV-related cancer is recommended for patients as per standard of care
☐	Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confi history of chickenpox or documentation 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 effect 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 in case suspicious lesions, potentially indicative of basal cell carcinoma, or other cutaneous neoplasms (including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma), are detected
☐	Provide patients, parents and caregivers with the Patient's, Parent's and Caregiver's Guide

Treatment Initiation Algorithm
All patients, including paediatric patients, need to be monitored for at least 6 hours during treatment initiation, as described in the algorithm below. This procedure should also be followed in paediatric patients when the dosage is switched from 0.25 mg to 0.5 mg Fingolimod once daily. It should also be followed at re-initiation of treatment if Fingolimod is discontinued for One day or longer within the first 2 weeks of treatment More than 7 days during weeks 3 and 4 More than 2 weeks after the first month of treatment In addition, for patients in whom Fingolimod is not recommended (see page 2), advice should be sought from a cardiologist regarding appropriate monitoring; at least overnight monitoring is recommended for this group.


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. The 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
Extend 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 in adults, <55 bpm in paediatric patients aged ≥12 years old, or <60 bpm in paediatric patients aged 10 to <12 years of age
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 by at least 2 hours and until heart rate increases
NO
First-dose monitoring is complete

During Treatment	
☐	A full ophthalmologic assessment is recommended: • 3–4 months after starting treatment for the early detection of visual impairment due to drug-induced macular oedema • During treatment in patients with diabetes mellitus or with a history of uveitis
☐	Counsel patients to report signs and symptoms of infection immediately to their prescriber 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. – Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2–3 years of treatment, although an exact relationship with the duration of treatment is unknown • Be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with Gemorya should be suspended until PML has been excluded – Cases of PML have occurred after approximately 2–3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown • Suspend treatment during serious infections
☐	Check full blood count periodically during treatment, at month 3 and at least yearly thereafter, and interrupt treatment if lymphocyte count is confirmed as <0.2x109/L*
☐	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 treatment discontinuation, or at any time there are signs or symptoms of hepatic dysfunction • 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 case of presence of clinical symptoms suggestive of hepatic dysfunction, the liver enzymes and bilirubin should be checked immediately and 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
☐	While on treatment, women should not become pregnant. Discontinue treatment if a woman becomes pregnant. Gemorya should be stopped 2 months before planning a pregnancy, and the possible return of disease activity should be considered. An ultrasonography examination should be performed and medical advice about the harmful effects of Gemorya to the foetus should be provided.
☐	Advise WOCBP (including adolescents and their parents/caregivers) that effective contraception must be used during treatment and for at least 2 months after treatment discontinuation. Pregnancy tests must be repeated at suitable intervals.
☐	WOCBP (including adolescents and their parents/legal representatives/caregivers) must be informed regularly about the serious risks of Gemorya to the foetus
☐	Ensure WOCBP (including adolescents), their parents (or legal representatives), and caregivers receive regular counselling facilitated by the Pregnancy-Specific Patient Reminder Card

☐	To help determine the effects of Gemorya exposure in pregnant women with MS, physicians are encouraged to report pregnant patients who may have been exposed to Gemorya at any time during pregnancy (from 8 weeks prior to last menstrual period onward) to Hikma by calling 00966114173731 Ext. 1086 or emailing SAPV@Hikma.com, in order to allow monitoring of these patients through enhanced pregnancy data collection.
☐	Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended with skin examination every 6 to 12 months and referral to a dermatologist if suspicious lesions are detected • Caution patients against exposure to sunlight without protection • Ensure patients are not receiving concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy
☐	Gemorya has an immunosuppressive effect and can increase the risk of developing lymphomas (including mycosis fungoides), and other malignancies (particularly those of the skin), and serious opportunistic infections. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Closely monitor patients during treatment, especially those with concurrent conditions, or known factors, such as previous immunosuppressive therapy; and discontinue treatment if a risk is suspected. Gemorya should be discontinued if lymphoma is suspected. Treatment discontinuation should be considered in those with a suspected risk on an individual basis.
☐	Cases of seizure, including status epilepticus, have been reported. Vigilance for seizures, especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy, is recommended
☐	Monitor paediatric patients for signs and symptoms of depression and anxiety
☐	Reassess on an annual basis the benefit of Gemorya treatment versus risk in each patient, especially paediatric patients

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 weeks 3 and 4 of treatment More than 2 weeks after one month of treatment
☐	Counsel patients to report signs and symptoms of infection immediately to their prescriber for up to 2 months after discontinuation Instruct patients to be vigilant for signs of meningitis infection and PML
☐	Inform WOCBP (including adolescents and their parents/caregivers) that effective contraception is needed for 2 months after discontinuation because of the serious risks of Fingolimod to the foetus
☐	Advise women who stop treatment with Fingolimod because they are planning a pregnancy that their disease activity may return
☐	Vigilance for the possibility of severe exacerbation of disease following discontinuation of treatment is recommended

Summary guidance specifically for paediatric patients

☐	Consider a complete vaccination schedule before starting Fingolimod
☐	Counsel patients and their parents/caregivers on Fingolimod's immunosuppressive effects
☐	Assess physical development (Tanner staging), and measure height and weight, as per standard of care
☐	Perform cardiovascular monitoring
☐	Perform first-dose monitoring on treatment initiation due to the risk of bradyarrhythmia
☐	Repeat first-dose monitoring in paediatric patients when the dosage is switched from 0.25 mg to 0.5 mg Fingolimod once daily
☐	Emphasize the importance of treatment compliance to patients, their parents and other caregivers, especially with regard to treatment interruption and the need to repeat first-dose monitoring
☐	Provide guidance on seizure monitoring
☐	Provide pregnancy-specific guidance including the Pregnancy-Specific Patient Reminder Card to adolescent patients of child-bearing potential and their parents/caregivers
☐	Paediatric patients should be monitored for symptoms of anxiety and depression

Call for Reporting

Adverse events should be reported.

Report adverse events to the National Pharmacovigilance and Drug Safety Centre (NPC)

Toll-free Phone: 19999

Email: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa

Fax: +966-11-205-7662.

Or

Report Adverse Events to Hikma Pharmaceuticals which includes Jazeera Pharmaceutical Industries (JPI), Arab Pharmaceutical Manufacturing (APM) and Hikma Farmacêutica

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