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- Instruct patients to report signs and symptoms of infections promptly to their prescriber during and for up to 3 months after discontinuation of treatment with ozanimod
 - Perform prompt diagnostic evaluation in patients with symptoms of infection while receiving or within 3 months of stopping treatment with ozanimod
 - Be vigilant for clinical symptoms including unexpected neurological or psychiatric symptoms or MRI findings that may be suggestive of progressive multifocal leukoencephalopathy (PML)
 - If PML is suspected a complete physical and neurological examination (including the possibility of performing an MRI) should be performed and withhold treatment with ozanimod until PML has been ruled out
 - If PML is confirmed, discontinue treatment with ozanimod
 - Immune reconstitution inflammatory syndrome (IRIS) has been reported in MS patients treated with S1P receptors modulators, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.
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Avoid administration of live attenuated vaccines during and for 3 months after discontinuation of treatment with ozanimod.

Check liver function (transaminase and bilirubin levels) at months 1, 3, 6, 9 and 12 during ozanimod therapy and periodically thereafter.

Blood pressure should be regularly monitored during treatment with ozanimod.

Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. Patients with diabetes mellitus, uveitis or a history of retinal disease should have follow up evaluations while receiving therapy.

ZEPOSIA® Healthcare Professional Information

ZEPOSIA® (ozanimod) Prescriber's Checklist

Important points to remember before, during,
and after treatment

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

For more information or to obtain a copy of this document, please contact Bristol-Myers Squibb by phone: 03-5231021, fax: 03-9226896 or email: Office_IL@bms.com.

Ozanimod Prescriber's Checklist

Patient Identification

Name: _____

Signature: _____

Date: _____

Prescriber Details

Name: _____

Signature: _____

Date: _____

Ozanimod is contraindicated in patients with the following:

- Immunodeficient state predisposing to systemic opportunistic infections
 - Severe active infections, active chronic infections such as hepatitis and tuberculosis
 - Active malignancies
 - Severe hepatic impairment (Child-Pugh class C)
 - Experienced in the last 6 months myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or New York Heart Association (NYHA) Class III/IV heart failure
 - History or presence of second-degree atrioventricular (AV) block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker
 - Pregnancy and in women of childbearing potential not using effective contraception
 - Hypersensitivity to the active substance or to any of the excipients.
- I confirm that none of these contraindications are applicable to this patient.

Prior to Treatment Initiation

- Consult a cardiologist before initiating treatment to determine if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy, when initiating ozanimod in patients with:
- History of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia
 - Pre-existing significant QT interval prolongation (QTc greater than 500 msec) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium-channel blockers that may potentiate bradycardia
 - Current class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products
- OR
- I confirm that a cardiology consult is not applicable to this patient
- Caution should be taken when initiating ozanimod in patients taking medicines known to decrease heart rate.

Before first dose:

- Obtain a baseline electrocardiogram (ECG) to determine whether any pre-existing cardiac abnormalities are present
 - Obtain recent (within last 6 months) liver function test results for transaminase and bilirubin levels
 - Obtain recent (within last 6 months or after discontinuation of prior therapy) complete blood cell count (CBC) results, including lymphocyte count
 - Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of varicella or documentation of a full course of varicella vaccination. If negative, VZV vaccination is recommended at least 1 month prior to treatment initiation with ozanimod.
 - Arrange an ophthalmological assessment before starting ozanimod treatment in patients with diabetes mellitus, uveitis, or a history of retinal disease
- OR
- I confirm that an ophthalmological assessment is not applicable for this patient

Pregnancy Counselling

- Give the patient card to women of childbearing potential and use it to counsel them on the risk of teratogenicity.
- Counsel women of childbearing potential to use effective contraception during treatment with ozanimod and for at least 3 months following treatment discontinuation
- Counsel women of childbearing potential to stop ozanimod at least 3 months before planning a pregnancy
- Counsel women of childbearing potential about the possible return of disease activity when stopping ozanimod therapy due to pregnancy or planning a pregnancy
- While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, ozanimod must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with ozanimod treatment and ultrasonography examinations should be performed

- Confirm a negative pregnancy test result in women of childbearing potential prior to starting treatment. It must be confirmed at suitable intervals
- OR
- I confirm that a pregnancy test and counselling on pregnancy precautions are not applicable to this patient
- Provide all patients/caregivers with the patient/caregiver guide, and with the patient card if appropriate
- OR
- Provision of patient card is not applicable to this patient

Treatment Initiation

Initiate treatment with a titration pack that lasts for 7 days. Start treatment with 0.23 mg once daily on Days 1-4, then increase the dose to 0.46 mg once daily on Days 5-7. Following the 7-day dose escalation, the once daily dose is 0.92 mg, starting on Day 8.

Patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) are recommended to complete the 7-day dose escalation regimen and then take 0.92 mg once every other day.

Re-initiation of Therapy Following Treatment Interruption

Use the same dose escalation regimen as initial treatment when treatment is interrupted for:

- 1 day or more during the first 14 days of treatment
- More than 7 consecutive days between Day 15 and Day 28 of treatment
- More than 14 consecutive days after Day 28 of treatment

If the treatment interruption is of shorter duration than the above, continue treatment with the next dose as planned.

Treatment Initiation Monitoring

First dose monitoring for 6 hours after first dose is required for certain patients.

- Patients with any of the following pre-existing conditions should be monitored for signs and symptoms of symptomatic bradycardia, with hourly pulse and blood pressure measurement for 6 hours after the first dose:
 - A resting heart rate <55 bpm
 - Second-degree [Mobitz type I] AV block
 - A history of myocardial infarction or heart failure
 - In these patients, perform an ECG prior to and at the end of this 6-hour monitoring period
- OR
- I confirm that this patient does not have applicable pre-existing cardiac conditions

Extended monitoring after 6 hours may be required in the following situations if at hour 6 post dose:

- Heart rate <45 bpm
- Heart rate is the lowest value post-dose, suggesting that the maximum decrease in heart rate may not have occurred yet
- Evidence of a new onset second-degree or higher AV block at the 6-hour post-dose ECG
- QTc interval ≥ 500 msec

In these cases, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If medical treatment is required, monitoring should be continued overnight, and a 6-hour monitoring period should be repeated after the second dose of ozanimod.

During Treatment and After Treatment Monitoring

Ozanimod reduces peripheral blood lymphocyte counts.

Complete blood cell count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored periodically during ozanimod treatment. Interrupt treatment if lymphocyte count is confirmed as $< 0.2 \times 10^9/L$ and the re-initiation of ozanimod can be considered if the level reaches $> 0.5 \times 10^9/L$.

Ozanimod has an immunosuppressive effect that predisposes patients to a risk of infection, including opportunistic infections, and may increase the risk of developing malignancies, particularly those of the skin.

- Carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, consider discontinuation of treatment on a case-by-case basis.
- Delay treatment initiation in patients with any severe active infection until the infection is resolved.
- Consider interruption of treatment during serious infections.
- Anti-neoplastic, immunomodulatory, or non-corticosteroid immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects
- Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended
 - Caution patients against exposure to sunlight without protection
 - Ensure patients are not receiving concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy