ZEPOSIA® (ozanimod) Prescriber's Checklist

Important points to remember before, during, and after treatment

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

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Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ZEPOSIA® should be discontinued. Patients with diabetes mellitus, uveitis or a history of retinal disease should undergo an ophthalmological evaluation prior to treatment initiation with ZEPOSIA® and have follow up evaluations while receiving therapy.

- ☐ Provide all patients/caregivers with the patient/caregiver Safety Information Guide, and with the pregnancy-specific patient reminder card if appropriate

You can report side effects directly to the Israeli Ministry of Health by using the on-line form for reporting adverse events on the Home page of the Ministry of health website: www.health.gov.il or by entering the following link: https://sideeffects.health.gov.il
You can also report side effects to BMS by phone: 1809-388-054 or email: MedInfo.Israel@BMS.com

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ZEPOSIA Healthcare Professional Information

ZEPOSIA® Prescriber's Checklist

Patient Identification

Name: _____

_____

_____

Prescriber Details

Name: _____

Signature: _____

Date: _____

Treatment Initiation

Initiate treatment with a treatment initiation 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 maintenance dose is 0.92 mg once daily, starting on Day 8.

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.

Prior to Initiating Treatment

☐ 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 multiple sclerosis [MS] therapy) complete blood cell count (CBC) results, including lymphocyte count

☐ Arrange an ophthalmological assessment before starting ZEPOSIA® treatment in patients with diabetes mellitus, uveitis or a history of retinal disease

☐ Confirm a negative pregnancy test result in women of childbearing potential prior to starting treatment. It must be confirmed at suitable intervals.

- ☐ I confirm that a pregnancy test is not applicable to this patient

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Until 6 hours after first dose for patients requiring first dose observation

☐ Monitor for signs and symptoms of symptomatic bradycardia, with hourly pulse and blood pressure measurement for patients with:

- A resting heart rate <55 bpm
- Second-degree [Mobitz type I] AV block
- A history of MI or heart failure

☐ Perform an ECG prior to and at the end of this 6-hour period

- ☐ 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:

- 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

☐ Consult a cardiologist before initiating treatment to determine if ZEPOSIA® can safely be initiated and to determine the most appropriate monitoring strategy, when initiating ZEPOSIA® 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

Caution should be taken when initiating ZEPOSIA® in patients taking medicines known to decrease heart rate.

- ☐ I confirm that a cardiology consult is not applicable to this patient

ZEPOSIA® 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.

During Treatment and After Treatment

ZEPOSIA® reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy). Monitor peripheral lymphocyte count periodically during ZEPOSIA® treatment. Interrupt treatment if lymphocyte count is confirmed as < 0.2 x 10^9/L and the re-initiation of ZEPOSIA® can be considered if the level reaches > 0.5 x 10^9/L.

ZEPOSIA® 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.
- Avoid co-administration of anti-neoplastic, immunomodulatory, or non-corticosteroid immunosuppressive therapies 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

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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 ZEPOSIA®

- Perform prompt diagnostic evaluation in patients with symptoms of infection while receiving or within 3 months of stopping treatment with ZEPOSIA®
- 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 ZEPOSIA® until PML has been excluded

If PML is confirmed, discontinue treatment with ZEPOSIA®

Avoid administration of live attenuated vaccines during and for 3 months after discontinuation of treatment with ZEPOSIA®. 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 ZEPOSIA®.

☐ Counsel women of childbearing potential about the serious potential risks of ZEPOSIA® to the foetus, facilitated by the pregnancy-specific patient reminder card and provide to appropriate patient and caregiver.

☐ Counsel women of childbearing potential to use effective contraception during treatment with ZEPOSIA® and for at least 3 months following treatment discontinuation

☐ Counsel women of childbearing potential to stop ZEPOSIA® at least 3 months before planning a pregnancy

☐ While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, ZEPOSIA® must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with ZEPOSIA® treatment and ultrasonography examinations should be performed.

☐ Women of childbearing potential should be informed about the possible return of disease activity when stopping ZEPOSIA® therapy due to pregnancy or planning a pregnancy

- ☐ I confirm that counselling on pregnancy precautions is not applicable to this patient

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

Blood pressure should be regularly monitored during treatment with ZEPOSIA®.

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