ZEPOSIA®
once-daily | ozanimod

Ozanimod (ZEPOSIA) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features

Clinical Protocol to Support Initiation

A practical guide for clinical teams initiating ZEPOSIA

Zeposia should be initiated under the supervision of a physician experienced in the management of patients with Multiple Sclerosis

Prescribing and adverse event reporting information can be found at the end of the document

Refer to the Summary of Product Characteristics before prescribing

2084-GB-2100041
March 2021

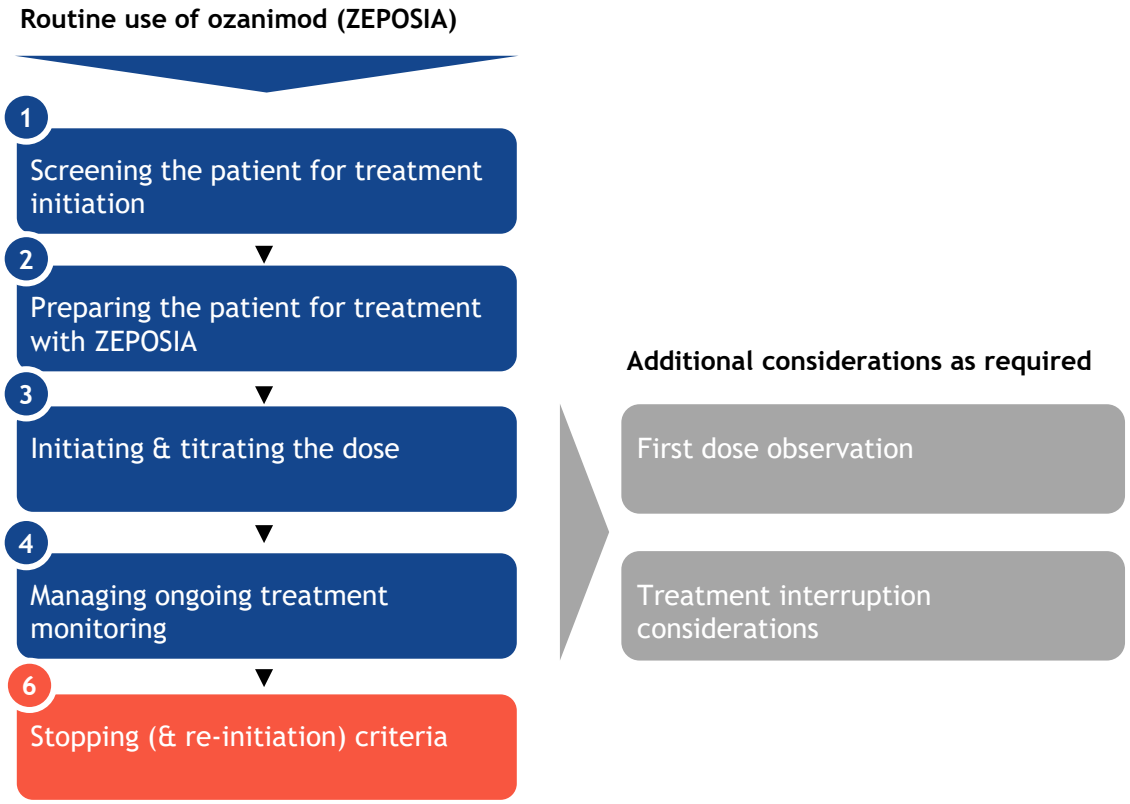
Bristol Myers Squibb™

Ozanimod (ZEPOSIA®▼) Protocol

Overview

This protocol provides a resource to NHS to support the initiation and monitoring of ozanimod (ZEPOSIA). Full prescribing information can be found on the final page of this document.

In accordance with the Summary of Product Characteristics (SmPC), it offers a set of instructions to support the use of ZEPOSIA in clinical practice. The protocol describes the steps shown below



Indication for treatment

Ozanimod (ZEPOSIA) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features

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1 Screening the patient for treatment initiation

Check for contraindications to ZEPOSIA use

Confirm that the patient:

- Has not **in the last 6 months** experienced 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
- Has no 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
- Has no previous hypersensitivity to ZEPOSIA or any excipients
- Has no active malignancies
- Is not in an immunodeficient state
- Has no severe or active chronic infection (hepatitis, tuberculosis)
- Has no severe liver impairment (Child-Pugh class C)
- Is not pregnant or is not breastfeeding and is using effective contraception. Women of childbearing potential must be counselled about the serious potential risks of ozanimod to the foetus

Required tests (before treatment initiation)

- Baseline echocardiogram (ECG)
- Liver function test (transaminase and bilirubin), or obtain results of a recent (within 6 months) liver test
- Complete blood cell count (CBC) including lymphocytes, or obtain results of a recent (within 6 months) CBC
- Pregnancy test in women of child-bearing potential not using contraception (N.B. ZEPOSIA is contraindicated in pregnancy)
- Patients with diabetes mellitus, uveitis or a history of retinal disease undergo an ophthalmological evaluation
- 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 first-dose-monitoring for patients with certain pre-existing cardiac conditions if required

First-dose, 6-hour observation for signs and symptoms of symptomatic bradycardia is recommended in patients with:

- resting HR <55 bpm
- second-degree [Mobitz type I] AV block
- history of myocardial infarction or heart failure

An ECG should be done before the first dose and at the end of the 6-hour monitoring period

Consider wider consultation for certain patients

A **cardiologist** should be consulted to determine safety of initiation and most appropriate monitoring before initiating ZEPOSIA in patients with history of cardiac arrest or cerebrovascular disease, uncontrolled hypertension, severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia, pre-existing significant QT interval prolongation or other risks for QT prolongation, or if currently on class Ia or class III antiarrhythmic treatments, or drugs other than beta-blockers / calcium channel blockers that may potentiate bradycardia.

Further monitoring after 6 hours is recommended in certain patients

Patients with any of the following conditions should be monitored beyond 6 hours:

- Heart rate <45 bpm;
- Heart rate is the lowest value post-dose, suggesting that the maximal decrease in heart rate may not have occurred yet;
- New onset second-degree or higher atrioventricular block on the 6-hour post-dose ECG;
- QTc interval ≥500msec.

Appropriate management should be initiated and observation continued until the symptoms/signs 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.

2 Preparing the patient for treatment with ZEPOSIA

Patient counselling should include benefits and potential side effects of ZEPOSIA plus stopping criteria

- Provide the patient with a **ZEPOSIA Information Pack** & ask to complete the screening checklist within it
- Review test results
- Review vaccination status of the patient; If live attenuated vaccine immunizations are required, these should be administered at least 1 month prior to initiation of ozanimod.
- Consider arranging a baseline MRI brain scan if required
- Refer for ophthalmology assessment 3-4 months after initiation if the patient has diabetes, uveitis or history of retinal disease
- Discuss first-dose observation, if required

3 Initiating & titrating the dose

An initial dose escalation regimen from day 1 to 7 is required and shown in the table below:

Days 1 - 4	0.23 mg once daily
Days 5 - 7	0.46 mg once daily
Days 8 and thereafter	0.92 mg once daily

- Contact pharmacy to arrange registration forms & prescription for Homecare delivery (if appropriate)
- Send a letter to the patient's GP to confirm ZEPOSIA has been commenced
- In case of the need for first dose observation see **'First dose observation'** section on the next page
- For treatment restart due to interruption see **'Treatment interruption considerations'** section on the next page

4 Ongoing treatment monitoring

Patient review should be conducted regularly to assess treatment progress and to monitor for any safety concerns that may require management, or suspension/discontinuation of ZEPOSIA*

Tests that should be periodically conducted are: (*see next section for stopping criteria)

- Liver function at 1,3, 6, 9 and 12 months and periodically thereafter
- CBC, including peripheral lymphocyte count
- Pregnancy (If the patient is a woman of childbearing potential)
- Blood pressure
- *Ophthalmological evaluation* - patients with diabetes, uveitis, history of retinal disease or visual symptoms of macular oedema

Vigilance should be adopted and observations made during reviews for:

- Signs and symptoms of infection
- Signs, symptoms (or MRI findings) suggestive of progressive multifocal leukoencephalopathy (PML)
- Signs and symptoms of posterior reversible encephalopathy syndrome (PRES)
- Signs of basal cell carcinoma or other cutaneous neoplasms

5

Stopping (& re-initiation) criteria

Stopping criteria should be made known to patients before treatment is initiated and includes:

Criteria	Re-initiation may be considered
1. Pregnancy	once breastfeeding has ceased
2. Reduction in lymphocyte count to <0.2x10^9 /L	if the level reaches > 0.5 x 109/l
3. Liver transaminases above 5 times the ULN	once liver transaminase values have normalised
4. Serious infection confirmed	infection confirmed as no longer present
5. Macular oedema	on resolution, if benefit outweighs risk for the patient
6. Suspected PML or PRES	if PML or PRES excluded

Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon discontinuation and appropriate treatment should be instituted as required.

Additional considerations (as required)

First dose observation

A 6-hour monitoring period following the first dose is required **only in patients who meet the criteria during screening**. The following should be done:

For the first 6 hours following administration of the first dose:

- Monitor for signs and symptoms of symptomatic bradycardia, with hourly pulse and blood pressure measurement
- Perform an ECG prior to and at the end of this 6-hour period

No abnormalities detected

Discharge patient home with 14-day supply of ZEPOSIA following the dose escalation regimen

Abnormalities detected

Additional monitoring is recommended in patients with:

- Heart rate <45 bpm
- Heart rate is the lowest value post-dose, suggesting that 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 this case, 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 ZEPOSIA

Treatment interruption considerations

Use the **same dose escalation regimen as initial treatment**, (including first-dose observation if applicable) when treatment is interrupted for:

- 1 day or more during the first 14 days of treatment

  or

- more than 7 consecutive days between Day 15 and Day 28 of treatment

  or

- more than 14 consecutive days after Day 28 of treatment.

If treatment interruption is of shorter duration than above, the treatment should be continued with the next dose as planned

Prescribing Information: ZEPOSIA® ▼ (ozanimod)

Refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Hard capsule containing ozanimod 0.23 mg, 0.46 mg and 0.92 mg.

Indications: ZEPOSIA® is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

Dosage and administration: Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis (MS). The recommended dose is 0.92 mg ozanimod once daily. The capsules can be taken with or without food. The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is required. Days 1-4 dose will be 0.23 mg once daily, Days 5-7 dose will be 0.46 mg once daily, Days 8 and thereafter maintenance dose will be 0.92 mg once daily. Refer to the SmPC for dosing recommendations and re-initiation of therapy following treatment interruption.

Special populations: *Adults over 55 years old and elderly population*: No dose adjustment needed and caution should be used in patients over 55 years of age. There are limited data available on RRMS patients > 55 years of age. *Renal and hepatic impairment*: No dose adjustment is necessary. *Paediatric population*: The safety and efficacy in children and adolescents aged below 18 years have not yet been established. See SmPC for further information on Special Populations.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Immunodeficient state. Patients who in the last 6 months experienced 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. Patients with 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.

Severe active infections, active chronic infections such as hepatitis and tuberculosis. Active malignancies. Severe hepatic impairment (Child-Pugh class C). During pregnancy and in women of childbearing potential not using effective contraception.

Special warnings and precautions: Bradyarrhythmia: *Initiation of treatment with ozanimod*: Prior to treatment initiation with ozanimod, an ECG in all patients should be obtained to determine whether any pre-existing cardiac abnormalities are present. In patients with certain pre-existing conditions, first-dose monitoring is recommended. Initiation of ozanimod may result in transient reductions in heart rate (HR) and therefore the initial dose escalation regimen to reach the maintenance dose (0.92 mg) on day 8 should be followed. After the initial dose of ozanimod 0.23 mg, the HR decrease started at Hour 4, with the greatest mean reduction at Hour 5, returning to near baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases. Heart rates below 40 beats per minute were not observed. If necessary, the decrease in HR induced by ozanimod can be reversed by parenteral doses of atropine or isoprenaline. Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (e.g. diltiazem and verapamil). Refer to SmPC for further information. *First dose monitoring in patients with certain pre-existing cardiac conditions:* Due to the risk of transient decreases in HR with the initiation of ozanimod, first-dose, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended in patients with resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure. Patients should be monitored with hourly pulse and blood pressure measurement during this 6-hour period. An ECG prior to and at the end of this 6-hour period is recommended. Additional monitoring after 6 hours is recommended in patients. Refer to SmPC for further information. *Cardiologist advice should be obtained before initiation of ozanimod in the following patients to decide if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy:* 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. Patients on class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products, which have been associated with cases of torsades de pointes in patients with bradycardia have not been studied with ozanimod. Liver function: Elevations of aminotransferases may occur in patients receiving ozanimod. Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with ozanimod. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ozanimod should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod. Ozanimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients. Refer to SmPC. Immunosuppressive effects: Ozanimod has an immunosuppressive effect that predisposes patients to a risk of infection and may increase the risk of developing malignancies, including those of the skin. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. Infections: Ozanimod causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of reversible retention of lymphocytes in the lymphoid tissues. Ozanimod may increase the susceptibility to infections. Assessments of CBC are also recommended periodically during treatment. Refer to SmPC. Prior and concomitant treatment with antineoplastic, immunosuppressive, or immune-modulating therapies: In MS clinical studies, patients who received ozanimod were not to receive concomitant antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ozanimod with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies would be expected to increase the risk of immunosuppression. Progressive multifocal leukoencephalopathy (PML)*: John Cunningham virus (JCV) infection resulting in PML has been observed in patients treated with MS therapies. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ozanimod should be discontinued. Vaccinations: No clinical data are available on the efficacy and safety of vaccinations in patients taking ozanimod. The use of live attenuated vaccines should be avoided during and for 3 months after treatment with ozanimod. If live attenuated vaccine immunizations are required, these should be administered at least 1 month prior to initiation of ozanimod. Varicella Zoster Virus (VZV) vaccination of patients without documented immunity to VZV is recommended prior to initiating treatment with ozanimod. Cutaneous neoplasms*: There is a potential risk of malignant skin growths, patients treated with ozanimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. Macular oedema: Macular oedema with or without visual symptoms was observed with ozanimod in patients with pre-existing risk factors or comorbid conditions. Patients with a history of uveitis or diabetes mellitus or underlying/co existing retinal disease are at increased risk of macular oedema. It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo an ophthalmological evaluation prior to treatment initiation with ozanimod and have follow up evaluations while receiving therapy. Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. A decision on whether ozanimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient. Posterior reversible encephalopathy syndrome (PRES)*: If PRES is suspected, treatment with ozanimod should be discontinued. Blood pressure effects. Blood pressure should be regularly monitored during treatment with ozanimod. Respiratory effects: Ozanimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Concomitant medicinal products: The coadministration with inhibitors of the breast cancer resistance protein (BCRP), inhibitors of monoamine oxidase (MAO), or CYP2C8 inducer (rifampin) with ozanimod is not recommended. Women of childbearing potential: Due to risk to the foetus, ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment, and for 3 months after treatment discontinuation. Return of disease activity (rebound) after ozanimod discontinuation: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping ozanimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon ozanimod discontinuation and appropriate treatment should be instituted as required.

**Serious adverse reaction*

Interactions: Effect of inhibitors of the breast cancer resistance protein (BCRP) on ozanimod: Coadministration of BCRP inhibitors (e.g. ciclosporin and eltrombopag) with ozanimod is not recommended. Effect of inhibitors of CYP2C8 on ozanimod: Caution should be exercised for concomitant use of ozanimod with strong CYP2C8 inhibitors (e.g. gemfibrozil, clopidogrel). Effect of inducers of CYP2C8 on ozanimod: Coadministration of CYP2C8 inducers (i.e., rifampin) with ozanimod is not recommended. Effect of inhibitors of monoamine oxidase (MAO) on ozanimod: Coadministration of MAO inhibitors (e.g., selegiline, phenelzine) with ozanimod is not recommended. Effects of ozanimod on medicinal products that slow heart rate or atrioventricular conduction (e.g., beta blockers or calcium channel blockers): Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker. Patients on other bradycardic medicinal products and on antiarrhythmic medicinal products (which have been associated with cases of torsades de pointes in patients with bradycardia) have not been studied with ozanimod. Vaccination: During and for up to 3 months after treatment with ozanimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should, therefore, be avoided during and for up to 3 months after treatment with ozanimod.

Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies: Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.

Fertility Pregnancy and lactation: See 'Special warnings and precautions' section for information on pregnancy. *Breast-feeding:* Breast-feeding should be discontinued during therapy with ozanimod. *Fertility:* No fertility data are available in humans.

Side effects: *Very common (≥ 1/10) or Common (≥ 1/100 to < 1/10) Adverse Drug Reactions reported in Multiple Sclerosis:* Alanine aminotransferase increased*, Blood bilirubin increased*, Bradycardia*, Gamma-glutamyl transferase increased*, Hypertension*, Lymphopenia, Nasopharyngitis, Orthostatic hypotension*, Pharyngitis, Pulmonary function test abnormal*, Respiratory tract infection viral*, Urinary tract infection*.

**Serious adverse reaction*

Other serious Adverse Drug Reactions: Hypersensitivity (including rash and urticaria), Macular oedema.

Prescribers should consult the SmPC in relation to other adverse reactions.

NHS list price: £343.25 per 7 capsule initiation pack (4 x 0.23 mg and 3 x 0.46 mg); £1,373.00 per 28 capsule 0.92 mg pack

Legal category: POM

Marketing authorisation numbers: Treatment initiation pack Zeposia 0.23 mg/ 0.46 mg hard capsules - EU/1/20/1442/001 (Pack size of 7 hard capsules). Maintenance pack - Zeposia 0.92 mg hard capsules - EU/1/20/1442/002 (Pack size of 28 hard capsules)

Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland

Adverse events should be reported. Reporting forms and information can be found at:
UK - MHRA under the Yellow Card Scheme website
www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Bristol-Myers Squibb via medical.information@bms.com or 0800 731 1736 (UK)

For further information contact:
medical.information@bms.com or 0800 731 1736 (UK)
Date of preparation: March 2021
Approval code: 2084-GB-2100040

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