Risk Management Plan – Prescriber's Checklist

Important points to remember before, during and after treatment with MAYZENT® ▼(siponimod)

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:

- the Yellow Card website **www.mhra.gov.uk/yellowcard**
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Adverse events should also be reported to Novartis via **uk.patientsafety@novartis.com** or online through the pharmacovigilance intake (PVI) tool at **www.novartis.com/report**.

Treatment with siponimod should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

This booklet has been created by Novartis Pharmaceuticals UK Limited and is intended for UK healthcare professionals only.

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Introduction

This checklist provides essential information on important risks associated with Mayzent treatment and the activities required to minimise these risks.

A patient and caregiver guide and a pregnancy reminder card for women of childbearing potential have also been developed as part of the risk minimisation plan, and may be used to inform your discussion with the patient. The patient guide can also support the early identification of signs and symptoms of potential adverse reactions, and their early treatment.

It is advised that this checklist is read alongside the Summary of Product Characteristics (SmPC) of Mayzent.

Careful consideration should be given to the information in the SmPC regarding patient selection before initiating treatment. The SmPC is available on the electronic medicines compendium (emc) website.

Therapeutic indication

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Important points to remember for patient selection

Patient selection

Prior to commencing treatment, the Mayzent maintenance dose of the patients must be determined by identifying their CYP2C9 enzyme genotype through a DNA sample obtained via blood or saliva sample (buccal swab):

- The test identifies variant alleles for CYP2C9
- Genotyping can be conducted using Sanger sequencing or a PCR assay based method. For further clarification please refer to your local laboratory

The recommended maintenance dose for all other genotypes, except CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3, is 2 mg daily. For patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3, the recommended maintenance dose is 1 mg. Mayzent is contraindicated in patients with a CYP2C9*3*3 genotype due to the risk of substantially elevated Mayzent plasma levels at therapeutic doses.

Contraindications

Mayzent is contraindicated in patients who have:

- Hypersensitivity to the active substance, or to peanut, soya or any of the excipients listed in the SmPC
- Immunodeficiency syndrome
- History of progressive multifocal leukoencephalopathy (PML) or cryptococcal meningitis (CM)
- Active malignancies
- Severe liver impairment (Child-Pugh class C)
- In the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure
- A history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker
- A homozygous CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser)
- During pregnancy and in women of childbearing potential not using effective contraception

Mayzent (siponimod) Prescriber's checklist

Complete fields or affix patient label

Patient's name: _____

Date of birth: _____

Patient identification number: _____

Treating healthcare professional: _____

Prior to initiating treatment

- ☐ Establish the correct Mayzent maintenance dose of the patients by identifying their CYP2C9 enzyme genotype through a blood or saliva test
  - Patients with CYP2C9*3*3 should not receive Mayzent
  - Patients with CYP2C9*1*3 or CYP2C9*2*3 should receive the 1 mg maintenance dose (following the titration schedule)
  - All other patients (CYP2C9 *1*1, *1*2, *2*2) should receive 2 mg (following the titration schedule)
- ☐ Check vitals and conduct a baseline electrocardiogram (ECG) in patients with a history of sinus bradycardia (heart rate [HR] <55 bpm), first or second-degree (Mobitz type I) AV block, or history of MI or heart failure (NYHA class I and II)
- ☐ Treatment with Mayzent is not recommended in the following patients, unless anticipated benefits outweigh the potential risks. A cardiologist must be consulted to determine appropriate monitoring and at least overnight extended monitoring is recommended when treatment is started.
  - Patients with uncontrolled hypertension, severe untreated sleep apnoea, recurrent syncope, symptomatic bradycardia, and in patients with significant QTc prolongation (>500 msec)
  - Patients receiving concurrent therapy with heart rate-lowering medicines such as Class Ia (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic drugs, calcium-channel blockers (e.g. verapamil, diltiazem) or other substances that are known to lower the heart rate (e.g. ivabradine, digoxin) during treatment initiation
- ☐ Establish whether the patient is taking a beta-blocker, and temporarily interrupt beta-blocker therapy in those whose baseline HR is ≤50 bpm until baseline HR is >50 bpm
  - Re-initiation of treatment with a beta-blocker can commence once Mayzent has been up-titrated to the target maintenance dose
- ☐ Siponimod should be used with caution in:
  - Elderly people with comorbidities or advanced disease or disability as the risk of bradyarrhythmia or infection may be increased during treatment;
  - Patients receiving anti-neoplastic, immunomodulators or immunosuppressants (including glucocorticoids) due to the risk of additive immune system effects.
- ☐ Check results of a recent full blood count and liver function tests (i.e. within 6 months or after discontinuation of prior therapy) and confirm as satisfactory
- ☐ Counsel patients to report signs and symptoms of liver dysfunction
- ☐ Do not initiate treatment with Mayzent in patients with severe active infection until infection is resolved
- ☐ Instruct patients to report signs and symptoms of infections immediately during treatment
- ☐ Check varicella zoster virus (VZV) antibody status in patients without a physician-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If negative, vaccination is recommended and treatment with Mayzent should be postponed for 1 month to allow the full effect of vaccination to occur
- ☐ Perform skin examination and be vigilant for skin malignancies
- ☐ Check results of an ophthalmologic evaluation prior to initiating therapy in patients with diabetes mellitus, uveitis or underlying/co-existing retinal disease and confirm as satisfactory
- ☐ Counsel patients to report visual disturbances at any time while on treatment
- ☐ Do not initiate treatment in patients with macular oedema until resolution
- ☐ Counsel patients on the importance of taking their daily dose, during titration and maintenance phases of treatment with Mayzent
- ☐ In women of childbearing potential, a negative pregnancy test is required prior to initiation of the treatment
- ☐ Counsel on the need for effective contraception in women of childbearing age during treatment and for at least 10 days following treatment discontinuation and advise of the potential serious risks to the foetus if Mayzent is used during pregnancy or the patient becomes pregnant whilst taking it
- ☐ **Provide patients with a Patient and Caregiver Guide**
- ☐ **Women of childbearing potential should also be provided with the Pregnancy Reminder Card**
- ☐ **Inform patients of the importance of reporting adverse events to either their doctor or directly to the Yellow Card scheme**

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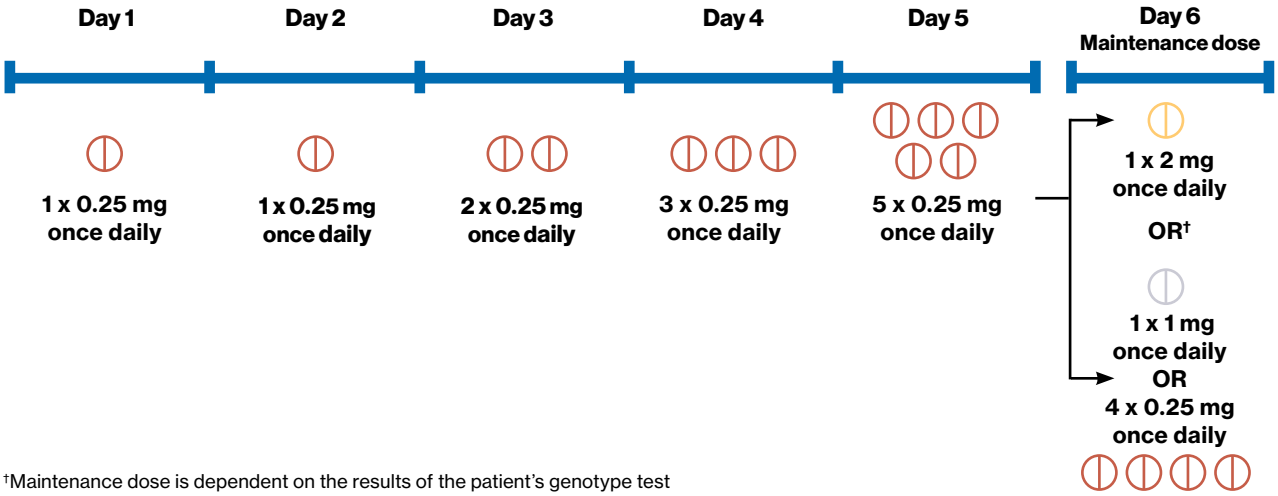
Treatment initiation schedule

Initiation of treatment with Mayzent results in a transient decrease in heart rate. For this reason, a 5-day up-titration scheme is required before a maintenance dose of 2 mg once daily can be achieved from Day 6 onwards (see figure). A titration pack containing 12 film-coated tablets in a wallet should be provided. In patients with a CYP2C9*1*3 or CYP2C9*2*3 genotype, the recommended maintenance dose is 1 mg once daily (starting on Day 6). Titration and maintenance doses can be taken with or without food.



†Maintenance dose is dependent on the results of the patient's genotype test

Important information

If a dose is missed on any day during the first 6 days of treatment, repeat the titration schedule with a new titration pack. Similarly, if treatment (maintenance dose) is interrupted for 4 or more consecutive days, treatment must be re-initiated with a new titration pack.

Treatment initiation: recommendations for patients with certain pre-existing cardiac conditions

Patients who have experienced an MI or Heart Failure NYHA class III/IV within the past 6 months should not be treated with Mayzent.

Mayzent causes transient heart rate reduction and may cause indirect AV conduction delays following initiation of treatment. Treatment initiation with a titration phase is usually well tolerated in most patients.

Patients with:

- sinus bradycardia (heart rate <55 bpm),
- first- or second-degree [Mobitz type I] AV block or
- a history of myocardial infarction (MI) or heart failure NYHA classes I and II

should be observed for signs and symptoms of bradycardia for a period of 6 hours after the first dose of Mayzent. Evaluation of ECG recordings both pre- and 6 hours post-dose is recommended. If necessary, the decrease in heart rate induced by Mayzent can be reversed by parenteral doses of atropine or isoprenaline.

☐ Perform baseline ECG and blood pressure (BP) measurement

▼

☐ Patient to take first titration dose

▼

☐ Monitor patients with certain pre-existing cardiac conditions for a period of 6 hours

Obtaining an ECG prior to dosing, and at the end of observation period is recommended

▼

☐ Did the patient develop post-dose bradyarrhythmia or conduction-related symptoms?

▶ YES

Initiate appropriate management

Continue to observe until the findings have resolved

▼

NO

☐ Did the patient require pharmacological intervention at any time during the monitoring period?

▶ YES

Monitor overnight in a medical facility and until the findings have resolved. Monitoring as for the first dose, should be repeated after the second dose of Mayzent

▼

NO

At the end of the 6-hour monitoring period, did ECG show:

☐ New-onset second-degree or higher AV block?

☐ QTc ≥500 msec?

▶ YES

Initiate appropriate management

Continue to observe until the findings have resolved

If pharmacological intervention is required, continue monitoring overnight and until the findings have resolved, and repeat 6-hour monitoring after the second dose.

▼

NO

☐ At the end of the 6-hour monitoring period, is the HR the lowest since the first dose was administered?

▶ YES

Extend monitoring by at least 2 hours and until the heart rate increases

▼

NO

First-dose monitoring is complete

The above first-dose monitoring procedure should be repeated in these patients if:

- A titration dose is missed on any day in the first 6 days
- Treatment is interrupted for >4 consecutive days during the maintenance phase

During treatment

- ☐ Conduct an ophthalmologic evaluation at 3–4 months after treatment
  - Conduct periodic ophthalmologic evaluations in patients with diabetes mellitus, uveitis, or a history of retinal disorders
  - Counsel patients to report any visual disturbance during treatment
- ☐ The full blood count should be repeated 3 to 4 months after starting siponimod treatment then monitored at least annually or checked if there are signs of an infection.
  - If the absolute lymphocyte count is confirmed as $<0.2 \times 10^9$/l, then the siponimod dose should be reduced to 1 mg daily.
  - If the absolute lymphocyte count is confirmed as $<0.2 \times 10^9$/l in a patient already receiving siponimod 1 mg daily, stop siponimod and only consider restarting it when the lymphocyte count has increased to at least 0.6×10^9/l.
- ☐ Counsel patients to report signs and symptoms of infection immediately to their prescriber
- ☐ Monitor patients carefully for signs and symptoms of infections:
  - Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; siponimod treatment should be suspended until exclusion; appropriate treatment of infection, if diagnosed, should be initiated
  - Cases of herpes viral infection (including cases of meningitis or meningoencephalitis caused by varicella zoster viruses) have occurred with siponimod at any time during treatment
  - Cases of cryptococcal meningitis have been reported for siponimod
  - Cases of PML have been reported for S1P receptor modulators, including siponimod, and other therapies for MS. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment should be suspended until PML has been excluded. If PML is confirmed, treatment with siponimod should be discontinued
- ☐ Exercise caution when administering concomitant treatment with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids), due to the risk of additive immune system effects
- ☐ Monitor for skin malignancies while on treatment with Mayzent
  - Patients treated with Mayzent should be cautioned against exposure to sunlight without protection
  - Perform skin examination every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected
  - Careful skin examinations should be maintained with longer treatment duration.
  - Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA photo-chemotherapy
- ☐ Should a patient develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, promptly schedule a complete physical and neurological examination and consider an MRI
- ☐ If patients develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia or jaundice and/or dark urine, they should have their liver function checked
  - Discontinue treatment if significant liver injury is confirmed
- ☐ Discontinue treatment if a patient becomes pregnant or is planning to become pregnant
  - Mayzent should be stopped at least 10 days before a pregnancy is planned. When stopping Mayzent therapy, the possible return of disease activity should be considered
- ☐ Counsel the patient in case of inadvertent pregnancy
- ☐ If a woman becomes pregnant whilst on treatment, they should be advised of potential serious risks to the foetus and an ultrasonography examination should be performed
- ☐ Should a pregnancy occur during treatment with Mayzent or within 10 days following discontinuation of treatment, regardless of it being associated with an adverse outcome, please also report it to Novartis Patient Safety via **uk.patientsafety@novartis.com** or **01276 698370** (standard call charge applies)

After discontinuation

- ☐ For patients who are eligible to restart Mayzent, repeat titration schedule with a new titration pack if:
  - A titration dose is missed on any day during the first 6 days or
  - Treatment is interrupted for ≥4 consecutive days during the maintenance phase
    - First-dose monitoring in specific patients will also need to be repeated as for treatment initiation (for more details please refer to the earlier section in this document regarding **recommendations for treatment initiation for patients with certain pre-existing cardiac conditions**)
- ☐ After discontinuation, Mayzent remains in the blood for up to 10 days
  - Exercise caution when starting other therapies during this time due to risk of additive effects
- ☐ If Mayzent is discontinued, the possibility of recurrence of high disease activity should be considered and the patient monitored accordingly
  - Counsel patients for possible worsening of MS after stopping Mayzent
- ☐ Instruct patients to report signs and symptoms of infections immediately and for up to one month after treatment discontinuation
- ☐ Counsel female patients that effective contraception is needed for at least 10 days after discontinuation. Should a pregnancy occur within 10 days after stopping Mayzent, regardless of it being associated with an adverse event or not, please also report it to Novartis Patient Safety via **uk.patientsafety@novartis.com** or by calling **01276 698370** (standard call charge applies)
  - Novartis has put in place a PRegnancy outcomes Intensive Monitoring (PRIM) programme, which is a registry based on enhanced follow-up mechanisms to collect information about pregnancy in patients exposed to siponimod immediately before or during pregnancy and on infant outcomes 12 months post-delivery

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