MAYZENT®▼

0.25 mg, 1 mg and 2 mg film-coated tablets (siponimod)

Physician's Checklist

Important points to remember before, during and after treatment with Mayzent®

▼ This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions of the medicinal product is important to Novartis and the HPRA. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported via HPRA Pharmacovigilance, website: www.hpra.ie. Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.

HPRA date of approval: 13/09/2023

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Contents

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.

This checklist is designed to be used alongside the approved summary of product characteristics (SmPC) of Mayzent®.

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.

Considerations for patient selection

Contraindications

Mayzent® is contradicted in patients who have:

- Hypersensitivity to the active substance, or to peanut, soya or any excipients listed in section 6.1 of 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)
- Become pregnant and in women of childbearing potential not using effective contraception

Not recommended

Mayzent® is not recommended in patients with:

- History of symptomatic bradycardia or recurrent sycope
- Uncontrolled hypertension
- Severe untreated sleep apnoea
- QTc prolongation >500msec
- Taking the following medications at treatment initiation
  - class 1a (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic drugs
  - calcium channel blockers (e.g. verapamil, dilitiazem)
  - other medications (e.g. ivabradine or digoxin) which are known to decrease the heart rate

Mayzent® treatment should only be considered in such patients if the anticipated benefits outweigh the potential risks and after consulting a cardiologist to determine the most appropriate monitoring strategy and possibility of switching to a non heart rate lowering drug before initiation of treatment.

Mayzent® treatment recommendations

The checklists and schematic that follow are intended to assist in the management of patients on Mayzent®. Key steps and considerations while initiating, continuing or discontinuing treatment are provided.

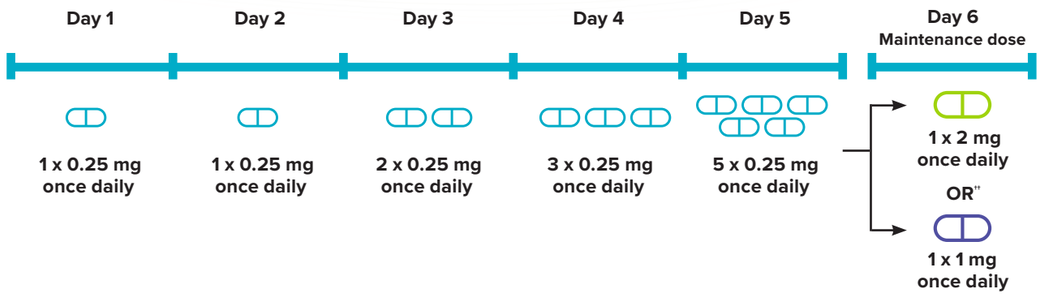
When selecting patients for treatment with Mayzent®ensure compliance with the contraindications and recommendations for non-treatment listed on the previous page.

Prior to initiating treatment

- ☐ Identify the CYP2C9 genotype of the patient to determine the correct Mayzent® maintenance dose. Genotyping can be conducted with a DNA sample obtained via saliva (buccal swab) using Sanger sequencing or PCR-based methods identifying variant alleles for CYP2C9
  - 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) can 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 1) AV block, or a history of myocardial infaction or heart failure if not contraindicated
- ☐ Caution should be exercised in elderly patients with multiple comorbidities, or advanced disease/ disability (due to possible increased risks of events such as infections or bradyarrhythmia during treatment initiation)
- ☐ Obtain recent (within 6 months) full blood count (CBC) and liver function tests (i.e. within 6 months or after discontinuation of prior therapy)
- ☐ Do not initiate treatment with Mayzent® in patients with severe active infection until it is resolved
- ☐ Take caution if patients are concomitantly treated with anti-neoplastic immunomodulatory or immunosuppresive therapies (including corticosteriods) due to the risk of additive immune system effects
- ☐ Instruct patients to report signs and symptoms of infections immediately during treatment
- ☐ Check varicella zoster virus (VZV) antibody status in patients without a physican's confirmed history of varicella or without documentation of a full course of varicella vaccination. If tested negative, vaccination is recommended and treatment with Mayzent® should be delayed for 1 month to allow full effect of vaccination to occur
- ☐ Counsel patients to report visual disturbances at any time while on treatment
- ☐ Arrange an ophthalmologic evaluation prior to initiating therapy in patients with diabetes mellitus, uveitis or underlying/co-existing retinal disease
- ☐ Do not initiate treatment in patients with macular oedema until resolved
- ☐ Perform skin examination and be vigilant for skin malignancies
- ☐ A negative pregnancy test result is required prior to initiation of treatment in women of childbearing potential
- ☐ Counsel women of childbearing potential about the serious risks of Mayzent® to the foetus and the need to use effective contraception during treatment and for at least 10 days following discontinuation of treatment facilitated by the pregnancy-specific patient reminder card.
- ☐ **Provide patients with a Patient and Caregiver Guide**
- ☐ **Women of childbearing potential should also be provided with the Pregnancy Reminder Card**
- ☐ Be familiar with the Mayzent® Prescribing Information
  - Inform patients of the importance of reporting adverse events to either their doctor or directly to Novartis

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 daily maintenance dose of 2 mg once daily can be achieved from Day 6 onwards (see figure). 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.



Important information

If a dose is missed on one 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.

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

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

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),
- a history of first- or second-degree [Mobitz type I] AV block or
- a history of myocardial infarction (MI) or heart failure* if not contraindicated must be observed for signs and symptoms of bradycardia for a period of 6 hours after the first dose of Mayzent®. Measurement of hourly vitals during this period and ECG measurements both pre- and 6 hours post-dose are recommended.

** Patients who have experienced an MI or heart failure within the past 6 months should not be treated with Mayzent®.*

☐ **Perform baseline ECG and BP measurement**

▼

☐ **Patient to take first titration dose**

▼

6hr ☐ **Monitor patients with cardiovascular risk for a minimum of 6 hours, with hourly pulse and BP checks**

▼

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

▼

NO

▶ **YES**

Initiate appropriate management

Continue to observe until the findings have resolved

If necessary, the decrease in heart rate induced by Mayzent® can be reversed by parenteral doses of atropine or isoprenaline

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

▼

NO

▶ **YES**

Monitor overnight in a medical facility.

Monitoring as for the first dose, should be repeated after the second dose of Mayzent®

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

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

☐ QTc >500 msec?

▼

NO

▶ **YES**

Initiate appropriate management

Continue to observe until the findings have resolved

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

6hr ☐ **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

First-dose monitoring is complete

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

- **A titration dose is missed for one day in the first 6 days**
- **Treatment is interrupted for 4 or more consecutive days during the maintanence phase**

During treatment

☐ An ophthalmologic evaluation at 3-4 months after treatment initiation is recommended in all patients
- 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

☐ Assessments of complete blood count are recommended 3–4 months following treatment initiation, and at least yearly thereafter, as well as in case(s) of signs of infection. If absolute lymphocyte counts < 0.2 x 109/L, reduce siponimod dose to 1 mg

– If absolute lymphocyte counts < 0.2 x 109/L in a patient already receiving siponimod 1 mg, temporarily stop treatment with siponimod until levels reaches 0.6 x 109/L. Re-initiation with siponimod may then be considered

☐ Monitor patients carefully for signs and symptoms of infections: Consider suspension of treatment in case of serious infection
- 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 (CM) have been reported for siponimod
- Cases of progressive multifocal leukoencephalopathy (PML) have been reported for S1P receptor modulators, including siponimod, and other therapies for MS. Physicians should be vigilant for clinical symptoms (e.g., weakness, visual changes, new/worsening symptoms of MS) 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 an anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) due to the risk of additive immune system effects.

☐ Be vigilant for skin malignancies while patients are on treatment with Mayzent®
- 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 be referred to a dermatologist if suspicious lesions are detected
- Patients should not receive concomitant phototherapy with UV-B radiation or PUVA- photochemotherapy.

☐ Should a patient develop any unexpected neurological or psychiatric symptoms/signs or accelerated deterioration, promptly schedule a complete physical and neurological examination, and consider an MRI

☐ If patients develop symptoms suggestive of hepatic dysfunction, request a liver enzymes check. 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 possibility return of disease activity should be considered
- Counsel women of childbearing potential regularly about the serious risks of Mayzent® to the foetus

☐ 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 with siponimod, regardless of it being associated with an adverse outcome, please report it to your doctor immediately or to Novartis.

☐ Caution patients against exposure to sunlight without protection

After discontinuation

☐ 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 maintanence phase First-dose monitoring in specific patients (patients with sinus bradycardia (HR <55 bpm), first- or second-degree AV block, or a history of MI or heart failure) will also need to be repeated

☐ 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. Instruct patients to report signs and symptoms of infection immediately 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 report it to Novartis by calling 01 208 0612 or emailing drugsafety.dublin@novartis.com
- 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 Mayzent® immediately before or during pregnancy, as well as infant outcomes 12 months post delivery

Further information For more detailed guidance on Mayzent®, please refer to the Summary of Product Characteristics (SmPC) available on www.medicines.ie

* Patients with sinus bradycardia (HR <55 bpm), first- or second-degree AV block, or a history of MI or heart failure.

August 2023 | IE_302974
HPRA date of approval: 13/09/2023