Prescriber's Checklist

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

NOVARTIS

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

Contents

Adverse drug reactions

Adverse drug reactions should be reported.

You can report any problem or adverse events or request additional copies of the materials through:

Patient Safety Department Novartis Pharma AG - Saudi Arabia -.

Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Or by online: https://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center

Unified Contact Center: 19999
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

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.

It is advised that this checklist is read 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

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 contradicted in patients who have:

- Hypersensitivity to the active substance, or to peanut, soya or to 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

Not recommended

Treatment with Mayzent® is not recommended in the following patients.

Consider Mayzent use only after performing risk/benefit analysis and 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.

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

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.

Prior to initiating treatment

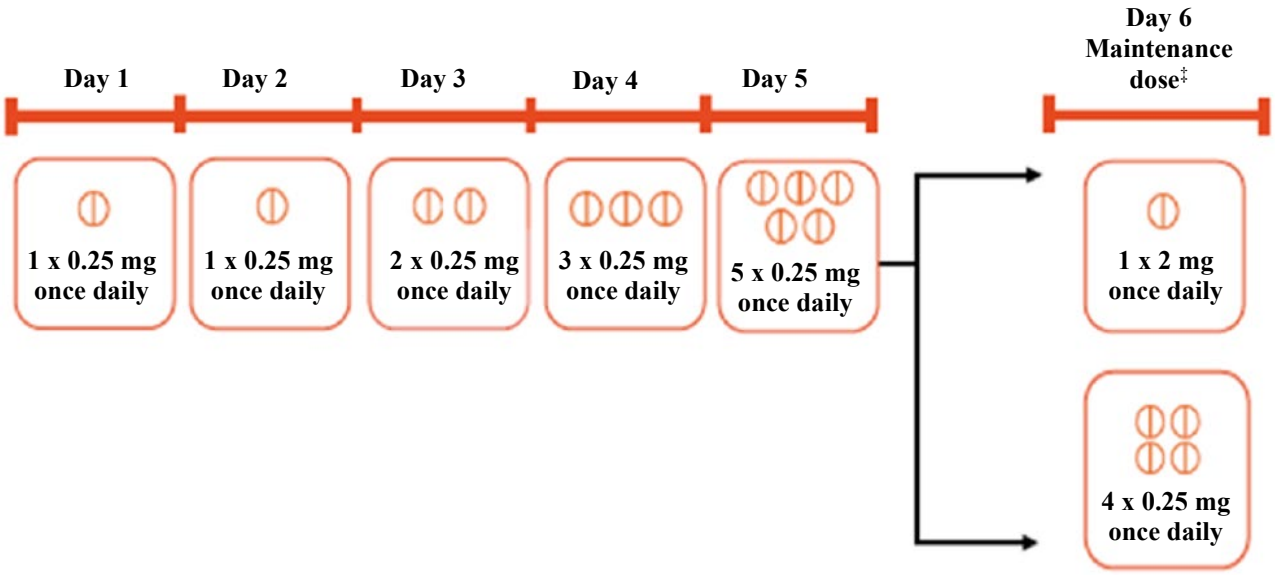
- Ensure to select patients according to contraindications and recommendations for non-treatment
- Identify the CYP2C9 genotype of the patient to determine the correct Mayzent® maintenance dose. Genotyping can be conducted with a DNA sample obtained via blood or saliva (buccal swab) using Sanger sequencing 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 I) AV block, or history of myocardial infarction or heart failure if not contraindicated
- Caution should be taken/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)
- Check availability of a recent complete 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 infection is resolved
- Take caution if patients are concomitantly treated with anti-neoplastic, immunomodulatory or immunosuppressive therapies (including corticosteroids) 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 physician-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If tested negative, vaccination is recommended and treatment with Mayzent® should be postponed for 1 month to allow the 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
- Perform skin examination and be vigilant for skin malignancies
- Do not initiate treatment in patients with macular oedema until resolution

- A negative pregnancy test result is required prior to initiation of treatment in women of childbearing potential and must be repeated at suitable intervals.
- 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 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 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

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 if not contraindicated

should 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. 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 cardiovascular risk for a minimum of 6 hours, with hourly pulse and BP checks

6hr

ECG measurements prior to dosing, and at the end of observation period are 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.
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 repeat 6-hour monitoring.

▼

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 or more consecutive days during the maintenance phase**

☐ During treatment

- An ophthalmological evaluation 3–4 months after treatment initiation is recommended
  - 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
  - If absolute lymphocyte counts < 0.2 x 109/L in a patient already receiving siponimod, 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:
  - 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
  - Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptor modulators, including siponimod, 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.
- 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
- Be vigilant for skin malignancies while on treatment with siponimod
  - Perform skin examination every 6 to 12 months taking into consideration clinical judgement
  - 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 neurological 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
- Counsel women of childbearing potential regularly about the serious risks of Mayzent® to the foetus
- 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 with siponimod, regardless of it being associated with an adverse outcome, please report it to SFDA, your doctor immediately or to Novartis.

☐ After discontinuation

- Repeat titration schedule with a new titration pack if treatment was discontinued by mistake and:
  - 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 (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 siponimod 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 infections 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 SFDA, your doctor immediately or to Novartis.

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

Further information

For more detailed guidance on Mayzent®, please refer to the Prescribing information: Summary of Product Characteristics (SmPC).