Mayzent®

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

Physician's Checklist*

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

Complete fields or affix patient label

Patient's name: _____

Date of birth: _____

Patient identification number: _____

Treating healthcare professional: _____

* This checklist may be used by physicians, nurses and pharmacists.

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Adverse event reporting

Adverse events associated with Mayzent® can be reported to the Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority at Tel: (65) 6866 1111, or report online at **https://www.hsa.gov.sg/adverse-events**

Adverse events should also be reported to Novartis –
Tel: **(65) 6722 6409** or email: **patientsafety.sg@novartis.com** or visiting **https://www.novartis.com/report**

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 Singapore package insert (PI) 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 to any of the excipients listed in the Package Insert
- 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

Treatment with Mayzent® is not recommended in the following patients. Consider Mayzent® only after performing risk/benefit analysis and consulting a cardiologist to determine the most appropriate monitoring strategy and possibility of switch 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 indication
  - class Ia (e.g. quinidine, procainamide) or class III (e.g. 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

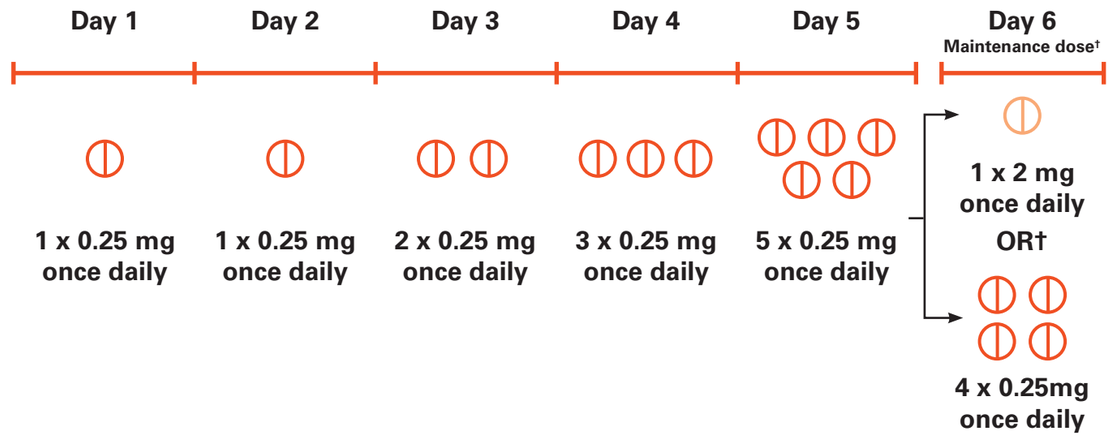
The checklists and schematic that follow are intended to assist in the management of patients on Mayzent®. Key steps and considerations while initiating, continuing or discontinuing treatment are provided.

Prior to initiating treatment

- ☐ Be aware of the contraindications and recommendations for non-treatment with Mayzent® when selecting appropriate patients who may benefit from the treatment
- ☐ Identify the CYP2C9 genotype of the patient to determine the correct Mayzent® maintenance dose. Genotyping can be conducted using a PCR assay based method identifying variant alleles for CYP2C9*2 and *3. For further clarification, please refer to your local laboratory
  - 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 without contraindications to Mayzent® treatment
- ☐ 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) (i.e. within last 6 months or after discontinuation of prior therapy); and transaminase and bilirubin levels (i.e. within last 6 months)
- ☐ Do not initiate of 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 initiation of 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.
- ☐ Do not initiate treatment in patients with macular oedema until resolution.
- ☐ 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. The Pregnancy Reminder Card may be used to faciliate discussion with the patient.
- ☐ **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 their doctor, pharmacist or nurse.**

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 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* without contraindications to Mayzent® treatment

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.

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

☐ 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
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 after the second dose

▼
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 maintanence phase

During treatment

☐ An ophthalmologic 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 periodically during treatment (e.g. 3–4 months following treatment initiation, and yearly thereafter), as well as in case(s) of signs of infection

- If absolute lymphocyte counts < 0.2 x 10^9/L, reduce siponimod dose to 1 mg
- If absolute lymphocyte counts < 0.2 x 10^9/L in a patient already receiving siponimod 1 mg, temporarily stop treatment with siponimod until levels reaches 0.6 x 10^9/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 leukoencephalo-pathy (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 anti-neoplastic immuno-modulating or immunosuppressive therapies (including corticosteroids) due to the risk of additive immune system effects

☐ Be vigilant for skin malignancies while on treatment with Mayzent®

- 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
- Caution patients against exposure to sunlight without protection
- 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 examinations 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 possible return of disease activity should be considered
- Counsel women of childbearing potential regularly 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

☐ 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 report it to Novartis by calling (65) 6722 6409, emailing at patientsafety.sg@novartis.com or visiting https://www.novartis.com/report

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 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 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 Novartis by calling (65) 6722 6409, emailing at patientsafety.sg@novartis.com or visiting https://www.novartis.com/report

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 full package insert.

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