

## Mayzent® | National Succinct Statement - Israel

**Important note:** Before prescribing, consult full prescribing information. **Presentation:** Tablets: 0.25 mg film-coated tablets corresponding to 0.25 mg siponimod, 2 mg film-coated tablets corresponding to 2 mg siponimod. **Indications:** Mayzent is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease, and active secondary progressive disease, in adults. **Posology and method of administration:** CYP2C9 genotype should be determined before initiation of treatment. Mayzent is contraindicated in patients with a CYP2C9\*3 genotype (approximately 0.3 to 0.4% of the population). Treatment initiation with a starter pack that lasts for 5 days. Once daily intake in the morning. On day 1 and 2: 0.25 mg. On day 3: 0.5 mg. On day 4: 0.75 mg. On day 5: 1.25 mg. Maintenance dose starts on day 6. **Adults:** Maintenance dose: 2 mg once daily. Oral use **Missed dose and re-initiation:** If a dose is missed on one day in the first 6 days of treatment or if 4 or more consecutive daily doses are missed during maintenance therapy, the same initial dose titration and monitoring recommendations should apply. **Special populations:** Maintenance dose for CYP2C9 \*2\*3 or \*1\*3 genotype: 1 mg once daily. Use with caution in the elderly. No dose adjustments are needed in patients with renal impairment or mild or moderate hepatic impairment. **Contraindications:** • Hypersensitivity to the active substance, or to peanut, soya or any of the excipients • Immunodeficiency syndrome • History of progressive multifocal leukoencephalopathy or cryptococcal meningitis • Active malignancies • Severe liver impairment (Child Pugh class C) • Patients who 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 • Patients with 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 • Patients homozygous for CYP2C9\*3 (CYP2C9\*3\*3) genotype (poor metaboliser) • During pregnancy and in women of childbearing potential not using effective contraception. **Special warnings and precautions for use:** • **Infections:** Before initiating treatment with Mayzent, a recent complete blood count (i.e. within last 6 months or after discontinuation of prior therapy) should be available. In patients with severe active infection, wait for resolution before initiating treatment. Effective diagnostic and therapeutic strategies should be used in patients with symptoms of infection while on therapy and up to 3 to 4 weeks after discontinuation (lowering effects on peripheral lymphocyte count). Consider discontinuing therapy if a serious infection develops. Vigilance for clinical symptoms of progressive multifocal leukoencephalopathy (PML) or cryptococcal meningitis (CM) is advised and if diagnosed, Mayzent treatment should be suspended. Patients without a physician-confirmed history of varicella or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV prior to treatment initiation. VZV vaccination is recommended in antibody-negative patients and initiation of treatment should be postponed for 4 weeks to allow the full effect of vaccination to occur. • **Macular edema:** Patients with history of uveitis and patients with diabetes mellitus are particularly at risk of developing macular edema. An ophthalmic examination is recommended 3 to 4 months after Mayzent therapy initiation and also before and regularly during therapy in patients at risk. Discontinuing therapy should be considered if macular edema develops. • **Treatment initiation:** Should not be used in patients with sino-atrial heart block (due to the risk of serious cardiac rhythm disturbances). Should not be used in patients with history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension or severe untreated sleep apnea (since significant bradycardia may be poorly tolerated in these patients). Use of Mayzent in these patients should be based on an overall benefit-risk assessment. Should not be used in patients with significant QT prolongation (QTc >500 msec). If treatment is being considered in patients with the aforementioned risk factors, pre-treatment consultation with a cardiologist is recommended to determine the most appropriate monitoring for treatment initiation. • Patients with sinus bradycardia (HR <55 bpm), first or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure if not contraindicated: patients should be observed for signs and symptoms of bradycardia for a period of 6 hours after the first dose. An ECG prior to dosing, and at the end of the 6-hour observation period is recommended. If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose. • **Liver function:** Recent transaminase and bilirubin levels should be available before initiation of treatment with Mayzent. A liver function test is recommended in patients who develop symptoms of hepatic dysfunction during treatment and therapy should be discontinued if significant liver injury is confirmed. • **Cutaneous neoplasms:** In phase 3 study, the incidence of basal cell carcinoma was 1.0% in Mayzent vs 1.2 % in placebo but additional cases have been reported with longer exposure to Mayzent. Cases of other skin malignancies, including melanoma, have also been reported. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer and patients with suspicious skin lesions. Patients treated with Mayzent should be cautioned against exposure to sunlight without protection and should not receive concomitant phototherapy with UV-B radiation or PUVA-phototherapy. • **Unexpected neurological signs:** Vigilance for any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration (PRES) is warranted. • **Blood pressure effect:** Blood pressure should be monitored during treatment with Mayzent and managed appropriately. • **Stopping therapy:** Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon Mayzent discontinuation and appropriate treatment should be instituted, as required. **Fertility, pregnancy and lactation:** **Pregnancy:** Mayzent is contraindicated during pregnancy. Embryotoxic, fetotoxic and teratogenic in animals. **Breast-feeding:** Should not be used during breast feeding. No data in human lactation. Passes into animal milk. **Women of childbearing potential/Contraception in females:** Mayzent is contraindicated in women of childbearing potential not using effective contraception. Women of childbearing potential must use effective contraception during treatment and for at least ten days following the last dose of Mayzent. **Undesirable effects: Very common (≥10%):** Headache, hypertension, liver function test increased. **Common (≥1 to <10%):** Herpes zoster, melanocytic naevus, basal cell carcinoma, lymphopenia, dizziness, seizure, tremor, macular oedema, bradycardia, atrioventricular block (1st & 2nd degree), nausea, diarrhoea, pain in extremity, oedema peripheral, asthenia, pulmonary function test decreased. **Frequency not known:** In the Extension Part of phase 3 study 2304, a case of cryptococcal meningitis has been reported. **Interactions:** • **Anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids):** Caution is required when used concomitantly with Mayzent and during the weeks following administration. Initiating treatment after alemtuzumab is not recommended unless the benefits clearly outweigh the risks. • **Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate:** At treatment initiation, concomitant use is not recommended with Class Ia (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmic drugs, QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g. verapamil or diltiazem) or other drugs that may lower heart rate (e.g. ivabradine or digoxin). If treatment is being considered in patients with the aforementioned risk factors, pre-treatment consultation with a cardiologist is recommended to determine the most appropriate monitoring for treatment initiation or regarding switching to a non-heart rate lowering drug • **Beta-blockers:** At treatment initiation, use with caution in patients receiving stable dose of beta-blocker if resting heart rate is ≤50 bpm. In this case, beta-blocker should be interrupted and restarted after up-titration to Mayzent maintenance dose. • **Vaccination:** Concomitant use is not recommended with live attenuated vaccines and for 4 weeks after stopping Mayzent therapy. Other vaccines may be less effective if administered during Mayzent treatment and treatment discontinuation 1 week prior to until 4 weeks after vaccination is recommended. • **CYP2C9 and CYP3A4 inhibitors:** Caution is required with moderate CYP2C9/CYP3A4 dual inhibitors (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor in all patients (an increase of siponimod exposure is expected). • **CYP2C9 and CYP3A4 inducers:** Caution is required with strong CYP3A4/moderate CYP2C9 dual inducers (e.g. rifampin or carbamazepine). Caution is also required with moderate inducers of CYP3A4 (e.g. modafinil) in patients with CYP2C9\*1\*3 and\*2\*3 (a reduction in siponimod exposure is expected). • **Oral contraceptives:** No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of siponimod on the efficacy of oral contraceptives is not expected. **Packs:** Mayzent 0.25 mg: titration packs of 12 film coated tablets, packs of 120 film coated tablets. Mayzent 2 mg: packs of 28 film coated tablets. **Legal classification:** prescription only. Feb. NSS 1.2021 based MAY API FEB21 V2



# MAYZENT®

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**

RMP 2021-004 ENG

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### Adverse drug reactions

Adverse events can be reported to the Ministry of Health via

<https://sideeffects.health.gov.il>

You may also report to the registration holder, Novartis Israel LTD. at:

[safetydesk.israel@novartis.com](mailto:safetydesk.israel@novartis.com)



## INTRODUCTION TO MAYZENT (SIPONIMOD)

This checklist provides essential information on important risks associated with Mayzent treatment and the activities required to minimize 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 minimization plan, and may be used to inform your discussion with the patient.

It is advised that this checklist is read alongside the approved prescribing information of Mayzent.

## THERAPEUTIC INDICATION

Mayzent is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease, and active secondary progressive disease, in adults.

## 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 PI
- 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 use 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 initiation
  - class Ia (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 test using Sanger sequencing or PCR-based methods identifying variant alleles for CYP2C9\*2 and \*3
  - 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 (NYHA class I and II) 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

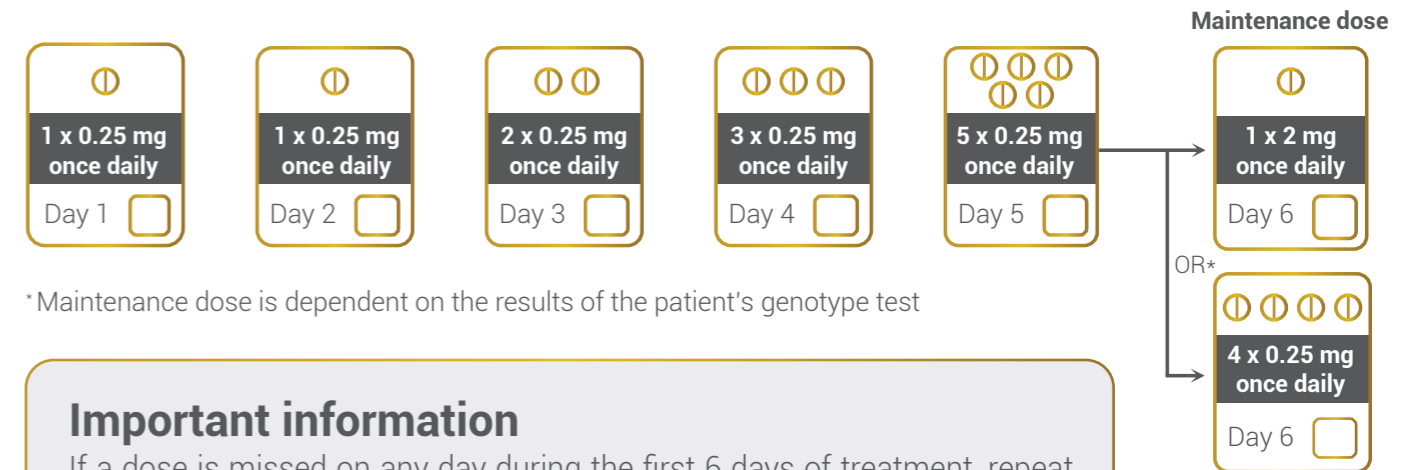


- Arrange an ophthalmologic evaluation prior to initiating therapy in patients with diabetes mellitus, uveitis or underlying/co-existing retinal disease
- Perform skin examination and be vigilant for skin malignancies
- Do not initiate treatment in patients with macular oedema until resolution
- A negative pregnancy test result is required prior to initiation of treatment in women of childbearing potential
- 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 directly or 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 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

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.

\* 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?



NO

▶ YES

Initiate appropriate management  
Continue to observe until the findings have resolved

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

**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.

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



NO

▶ 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 on any day in the first 6 days
- Treatment is interrupted for >4 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 periodically during treatment
- Monitor patients carefully for signs and symptoms of infections:
  - Consider suspension of treatment in case of serious infection
  - Perform prompt diagnostic evaluation in patients with symptoms and signs (including MRI findings) consistent with CM and PML. If CM or PML is suspected, treatment should be suspended until PML or CM has been excluded. Appropriate treatment, if diagnosed should be initiated.
- Exercise caution when administering concomitant treatment with anti-neoplastic, immunomodulating 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. Patients should be referred to a dermatologist if suspicious lesions are detected
  - Patients should not receive concomitant phototherapy with UV-B radiation or PUVA-chemotherapy.
- 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.
- 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, counsel patients to report it to their prescriber immediately or to Novartis at: [safetydesk.israel@novartis.com](mailto:safetydesk.israel@novartis.com)



## After discontinuation

- Repeat titration schedule with a new titration pack if treatment was discontinued by mistake:
  - A titration dose is missed on any day during the first 6 days
  - Treatment is interrupted for  $\geq 4$  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 counsel patients to report it to their prescriber immediately or to Novartis at [safetydesk.israel@novartis.com](mailto:safetydesk.israel@novartis.com)

Novartis has put in place a PRenancy outcomes Intensive Monitoring (PRIM) program, 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 (PI). The PI, the Patient and Caregiver Guide, the Pregnancy Reminder Card and the Physician's Checklist are all available at

<https://data.health.gov.il/drugs/index.html#!/medDetails/165%2055%2036196%2000>  
or <https://data.health.gov.il/drugs/index.html#!/medDetails/165%2054%2036195%2000>

This document has been determined by the Ministry of Health and the content therefore has been checked and approved on May 2021

