Mayzent
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 a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease, and active secondary progressive disease, in adults. Dosage and administration:** CYP2C9 genotype should be determined before initiation of treatment. Mayzent should not be used in patients with a CYP2C9*3*3 genotype. 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: 2 mg. **Adults:** Maintenance dose: 2 mg once daily. **Special populations:** •Maintenance dose for CYP2C9 *2*3 or *1*3 genotype: 1 mg once daily treatment initiation On day 1 and 2: 0.25 mg. On day 3: 0.5 mg. On day 4: 0.75 mg. Do not use the starter pack for patients who will be titrated to the 1-mg maintenance dosage. •No dose adjustments are needed in patients with renal or hepatic impairment or in geriatric patients (65 years or above). **Contraindications:** With patient who have: •A CYP2C9*3/*3 genotype •in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure **•Presence of Mobitz type II second-degree, third degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker.Warnings and precautions: •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. igilance 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 healthcare professional 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 1 month 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 evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.. Discontinuing therapy should be considered if macular edema develops. **•Treatment initiation:** Should not be used in patients with second-degree Mobitz type II or higher AV block, sick-sinus syndrome or sino-atrial heart block (due to the risk of serious cardiac rhythm disturbances). Should not be used in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea (since significant bradycardia may be poorly tolerated in these patients). Should not be used in patients with significant QT prolongation (QTc >500 msec). In patients with a history of recurrent syncope or symptomatic bradycardia, use of Mayzent should be based on an overall benefitrisk assessment. 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. **• Bradyarrhythmia and Atrioventricular Conduction Delays:** 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: 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. Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs **•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. **•Respiratory Effects:** Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MAYZENT- treated patients as early as 3 months after treatment initiation. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated **•Liver Injury:** 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. **•Increased BloodPressure:** Blood pressure should be monitored during treatment with MAYZENT and managed appropriately. **•Unexpected neurological signs:** Vigilance for any unexpected neurological or psychiatric symptoms/signs of accelerated neurological deterioration (PRES) is warranted. •Pharmacogenomics: Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.4 to 0.5% of Caucasians and less in others) should not be treated with Mayzent. **•Immune System Effects After Stopping MAYZENT:** other therapies during this interval will result in concomitant exposure to siponimod. •Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended. •Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required. After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting •The tablets contain lactose.**Pregnancy, lactation, females and males of reproductive potential •Pregnancy:** Not recommended unless benefits outweigh risks. No data in human pregnancy. Embryotoxic, fetotoxic and teratogenic in animals. **Lactation:** Not recommended. No data in human lactation. Passes into animal milk. **Females and males of reproductive potential:** Effective contraceptive measures are recommended in women of child-bearing potential during treatment with Mayzent and for at least 10 days after stopping treatment. **Adverse drug reactions: •Headache** (tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache). **•Hypertension** (blood pressure increased, blood pressure systolic increased, essentialhypertension, blood pressure diastolic increased), **•Transaminase increased** (alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased), **•Falls, •Edema peripheral** (edema peripheral, joint swelling, fluid retention, swelling face), **•Bradycardia** (sinus bradycardia, heart rate decreased), •Pain in extremity and limb discomfort, •seizure, •pulmonary function test decreased , •Vascular events (ischemic strokes, pulmonary embolisms, and myocardial infarctions), **• Malignancies** (malignant melanoma in situ and seminoma) •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, pretreatment 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 a planned vaccination is recommended. **•CYP2C9 and CYP3A4 inhibitors:** Caution is required with moderate CYP2C9/CYP3A4 inhibitors (e.g. fluconazole) in patients with CYP2C9*2*2 or dosage adjustment to Mayzent 1 mg daily may be considered (approximately 2.7-fold increase of siponimod exposure is expected). **•CYP2C9 and CYP3A4 inducers:** Caution is required with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients and 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 OCs containing other progestagens; however, an effect of siponimod on their exposure is not expected.
Packs and prices: Country-specific.
Legal classification: Country-specific.
Tracking No.: Initial Labeling Package.
Version No.: V1.0

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
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Or by online: https://report.novartis.com/

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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®

Before local implementation, you must ensure compliance with all applicable laws and regulations, including local industry codes, as well as local Novartis companies' policies. Before release, the final piece must be submitted to and approved by the local EU competent authority where applicable.

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"This checklist is suitable for physicians and nurses"

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Adverse drug reactions

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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:
  - Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent ith 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 with another sphingosine 1-phosphate (S1P) receptor modulator. 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
- ☐ 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 s 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 your doctor immediately or to Novartis by calling

Novartis Saudi Arabia.
Phone: +96611 265 8100
Fax: +966 11 265 8107
Email: adverse.events@novartis.com
https://psi.novartis.com/

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 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 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 famale 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 your doctor immediately or to Novartis:

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- ☐ 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) available at https://www.psi.novartis.com/
The SmPC, the Patient and Caregiver Guide, the Pregnancy Reminder Card and the Physician's Checklist are all available at https://www.psi.novartis.com/

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 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 seconddegree 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 days or more consecutive days during the maintanence phase

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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.

It is advised that this guide 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

Contraindications

Mayzent® is contradicted in patients who have:

- Hypersensitivity to the active substance, 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 myocardia 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 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 or saliva (buccal swab) 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 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)
- ☐ 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 to directly to Novartis

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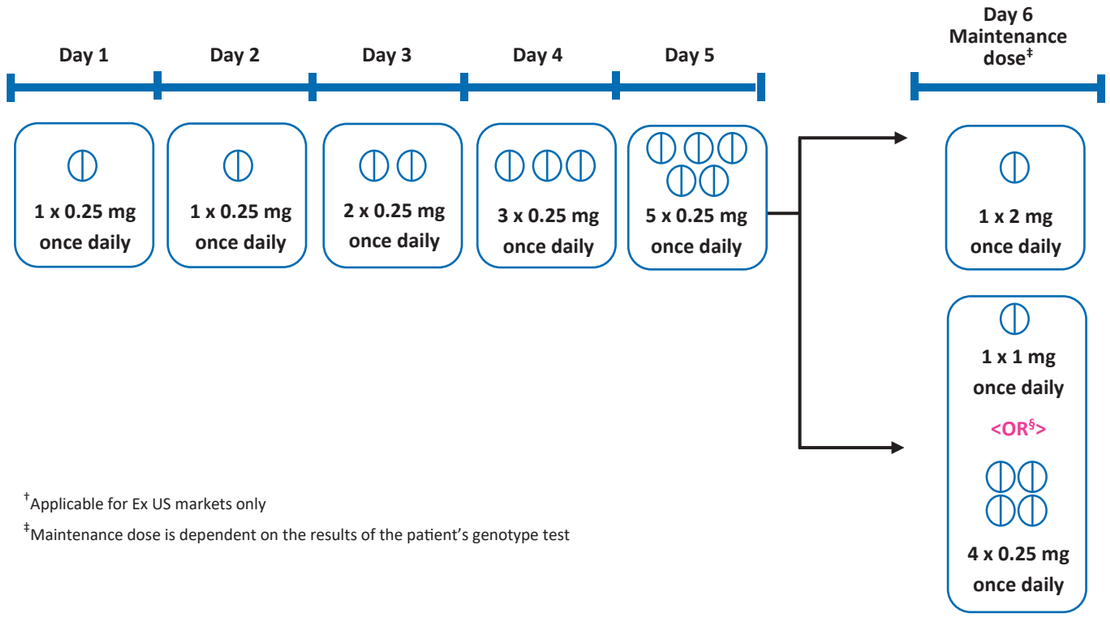
Treatment initiation schedule†

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.



†Applicable for Ex US markets only

‡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.