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®

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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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.

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

## 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 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

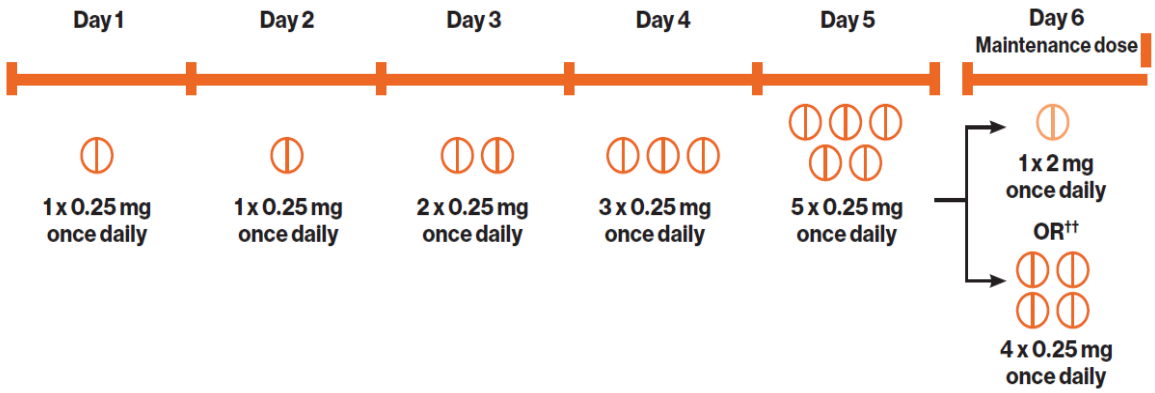
- Ensure to select patients according to contraindications and recommendations for non-treatment
- Identify the CYP2C9 genotype of the patient to determine the correct Mayzent® maintenance dose. Genotyping can be conducted with a DNA sample obtained via blood or saliva (buccal swab) using Sanger sequencing 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 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 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 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**

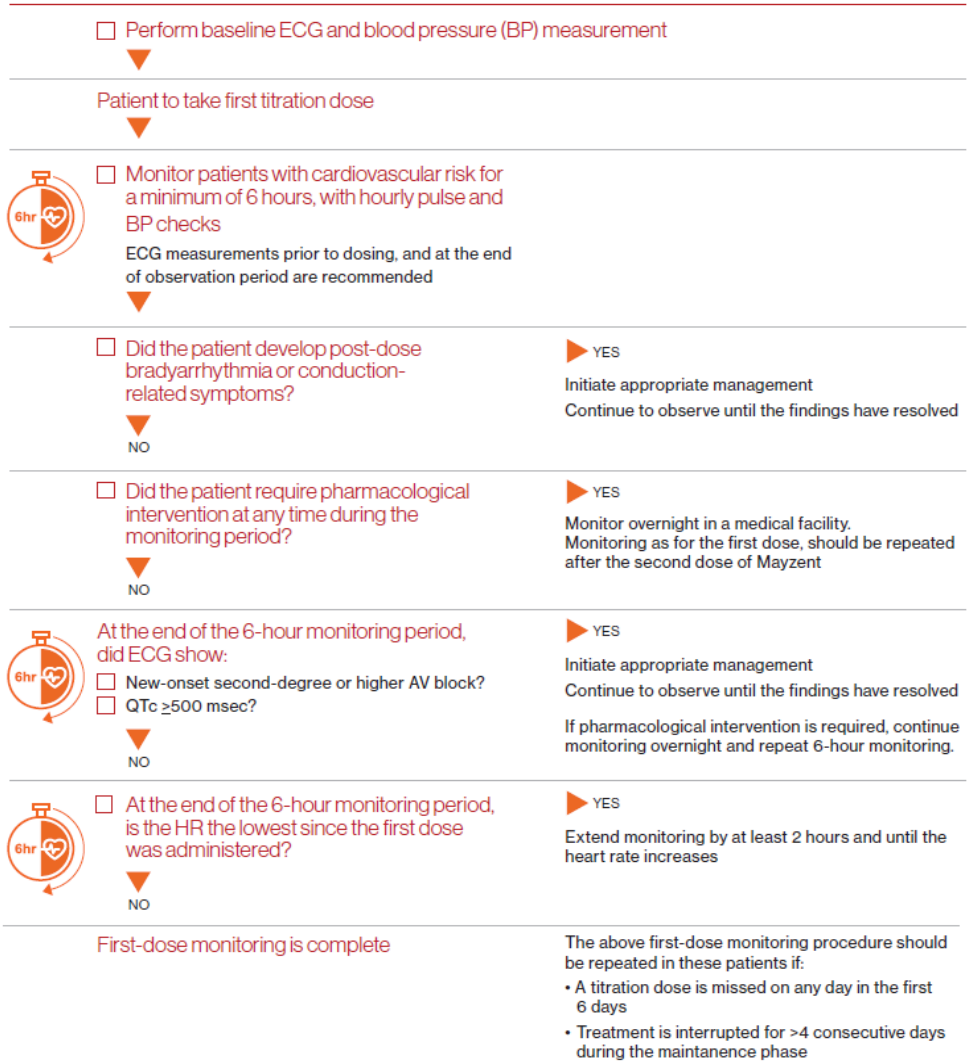
If a dose is missed on any day during the first 6 days of treatment, repeat the titration schedule with a new titration pack. Similarly, if treatment (maintenance dose) is interrupted for 4 or more consecutive days, treatment must be re-initiated with a new titration pack.

# 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.



## 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, 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 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 your doctor immediately or to Novartis by calling +35621222872 or visiting www.report.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 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 your doctor immediately or to Novartis by calling +35621222872 or visiting www.report.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 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.ema.europa.eu/en/medicines/human/EPAR/mayzent >.

The Patient and Caregiver Guide, the Pregnancy Reminder Card and the Physician's Checklist are all available at http://www.medicinesauthority.gov.mt/rmm

## Mayzent®

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

**PRESENTATION**:
♦0.25mg film-coated tablets: 0.25 mg siponimod). each film-coated contains siponimod fumaric acid (equivalent to
♦2mg film-coated tablets: each film-coated tablet contains siponimod fumaric acid (equivalent to 2 mg siponimod).

**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.

**DOSAGE:** Treatment should be initiated and supervised by a physician experience in the management of multiple sclerosis. Mayzent is for oral use. It should be taken with or without food and the tablets should be swallowed whole with water. ♦Treatment initiation: Treatment has to be started with a titration pack that lasts for 5 days. Treatment starts with 0.25 mg once daily on days 1 and 2, followed by once-daily doses of 0.5 mg on day 3, 0.75 mg on day 4, and 1.25 mg on day 5, to reach the patient's prescribed maintenance dose of siponimod starting on day 6. During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food. ♦Special populations: ♦ Elderly: Siponimod has not been studied in patients aged 65 years and above. Clinical studies included patients up to the age of 61 years. Siponimod should be used with caution in the elderly due to insufficient data on safety and efficacy. ♦ Renal impairment: Based on clinical pharmacology studies, no dose adjustment is needed in patients with renal impairment. ♦ Hepatic impairment: Siponimod must not be used in patients with severe hepatic impairment (Child-Pugh class C). Although no dose adjustment is needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients. ♦ Paediatric population: The safety and efficacy of siponimod in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

**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, ♦ Patients who in the previous 6 months had: myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attach, decompensated heart failure, ♦ Patients with a history of second-degree Mobitz type II atrioventricular block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker, ♦ Patients homozygous for CYP2C9*3 genotype, ♦ During pregnancy and in women of childbearing potential not using effective contraception.

**WARNINGS/ PRECAUTIONS:** ♦ Effects on ability to drive and use machines: Siponimod has no or negligible influence on the ability to drive and use machines. However, dizziness may occasionally occur when initiating therapy with siponimod. Therefore, patients should not drive or use machines during the first day of treatment initiation with siponimod. ♦Infections: the immune system effects of siponimod may increase the risk of infections. Before initiating treatment, a recent complete blood count (within last 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment. Initiation of treatment should be delayed in patients with severe active infection until resolution. Patients should be instructed to report symptoms of infection to their physician promptly. Suspension of treatment with siponimod should be considered if a patient develops a serious infection. ♦ Vaccination: A full course of vaccination with varicella vaccine is

recommended for antibody negative patients prior to commencing treatment with siponimod, following which initiation of treatment should be postponed for 1 month to allow the full effect of vaccination to occur. The use of live attenuated vaccines should be avoided while patients are taking siponimod and for 4 weeks after stopping treatment. Vaccinations may be less effective if administered during siponimod treatment. Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. When stopping siponimod therapy for vaccination, the possible return of disease activity should be considered. ♦ Macular oedema: Siponimod therapy should not be initiated in patients with macular oedema until resolution. Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema. It is recommended that these patients should undergo an ophthalmological evaluation prior to initiating therapy and regularly while receiving siponimod therapy to detect macular oedema. Continuation of siponimod therapy in patients with macular oedema has not been evaluated. It is recommended that siponimod be discontinued if a patient develops macular oedema. A decision on whether or not siponimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient. ♦ Bradyarrhythmia: As a precautionary measure, patients with the following cardiac conditions should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia:sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block, history of myocardial infarction, or history of heart failure (patients with NYHA class I and II). In these patients, it is recommended that an electrocardiogram (ECG) is obtained prior to dosing and at the end of the observation period. Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, siponimod should not be used in patients with: history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension, or severe untreated sleep apnoea. In such patients, treatment with siponimod should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy. ♦ Liver function: recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with siponimod. ♦ Cutaneous neoplasms: Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. ♦ Unexpected neurological or psychiatric symptoms/signs:should a patient on siponimod treatment develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled and MRI should be considered. ♦ Prior treatment with immunosuppressive or immune-modulating therapies: caution should be exercised during concominant administration of any of these medicinal products is stopped. ♦ Blood pressure effects: Blood pressure should be regularly monitored during treatment with siponimod. ♦ CYP2C9 genotype: Before initiation of treatment with siponimod, patients should be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. Patients homozygous for CYP2C9*3 should not be treated with siponimod. ♦ Stopping siponimod therapy: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping siponimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon siponimod discontinuation and appropriate treatment should be instituted as required. After siponimod therapy has been stopped, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod. ♦ Interference with haematological testing: Since siponimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with siponimod. ♦ Excipients: The tablets contain soya lecithin. Patients

who are hypersensitive to peanut or soya should not take siponimod. The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**INTERACTIONS:** ♦ Antineoplastic, immune-modulating or immunosuppressive therapies: Siponimod has not been studied in combination with antineoplastic, immune-modulating or immunosuppressive therapies. Caution should be exercised during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks after administration of any of these medicinal products is stopped. ♦ Anti-arrhythmic medicinal products, QT-prolonging medicinal products, medicinal products that may decrease heart rate: During treatment initiation siponimod should not be concomitantly used in patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate. If treatment with siponimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate-lowering medicinal products or appropriate monitoring for treatment initiation. ♦Beta blockers: Caution should be exercised when siponimod is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate. Beta blocker treatment can be initiated in patients receiving stable doses of siponimod.♦ Vaccination: The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during siponimod treatment and for up to 4 weeks after treatment. During and for up to 4 weeks after treatment with siponimod vaccinations may be less effective. The efficacy of vaccination is not considered to be compromised if siponimod treatment is paused 1 week prior to vaccination until 4 weeks after. ♦ CYP2C9 and CYP3A4 inhibitors: Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor. ♦ CYP2C9 and CYP3A4 inducers: Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. ♦ Oral contraceptives: Co-administration with siponimod did not reveal clinically relevant effects on the pharmacokinetics and pharmacodynamics of the combined ethinylestradiol and levonorgestrel oral contraceptive. Therefore the efficacy of the investigated oral contraceptive was maintained under siponimod treatment. 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.

**PREGNANCY, LACTATION AND FERTILITY:** ♦ Women of childbearing potential/Contraception in females: Siponimod is contraindicated in women of childbearing potential not using effective contraception. Before initiation of treatment in women of childbearing potential a negative pregnancy test result must be available and counselling should be provided regarding serious risk to the foetus. Women of childbearing potential must use effective contraception during treatment and for at least ten days following the last dose of siponimod ♦ Pregnancy: Siponimod is contraindicated in pregnancy. Siponimod should be stopped at least 10 days before a pregnancy is planned. If a woman becomes pregnant while on treatment, siponimod must be discontinued. ♦ Lactation: Siponimod should not be used during breast-feeding. ♦ Fertility: The effect of siponimod on human fertility has not been evaluated.

**ADVERSE REACTIONS**: increase. Very Common (≥1/10): Headache, Hypertension, Liver function test Common (≥1/100 to <1/10): Herpes zoster, Melanocytic naevus, Basal cell carcinoma, lyphopenia, dizziness, seizure, tremor, macular oedema, bradycardia, atrioventricular block (frist and second degree), nausea, diarrhoea, pain in extremity, oedema peripheral, asthenia, pulmonary function test decreased.

**LEGAL CATEGORY**: POM

**PACK SIZES**: 0.25mg: Titration packs of 12 film-coated tablets, Packs of 120 film-coated tablets.2mg: Packs of 28 film-coated tablets.

**MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

**MARKETING AUTHORISATION NUMBERS:**
Mayzent 0.25 mg film-coated tablets: EU/1/19/1414/001-002.
Mayzent 2 mg film-coated tablets: EU/1/19/1414/003

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

**2021MTMAY07Jan2**

**Suspected Adverse Drug Reactions** (side effects) and medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to;

**P:** Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann. SGN 3000.

**E:** postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events associated with the use of **Mayzent** to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, online on www.report.novartis.com or by e-mail at drug_safety.malta@novartis.com.

Marketing Authorization Holder: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Local Representative: Novartis Pharma Services Inc., Representative Office Malta.

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**For electronic copies of this Educational Material, please refer to the Malta Medicines Authority website -** http://www.medicinesauthority.gov.mt/rmm **- and download the required material with the latest date.**

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