Prescribing Information: Mayzent®▼ (siponimod)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Film-coated tablets containing 0.25 mg or 2 mg siponimod (as siponimod fumaric acid). **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 and administration:** Treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Before treatment initiation, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. In patients with a CYP2C9*3*3 genotype, siponimod should not be used. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily. The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg. Siponimod is taken orally once daily, with or without food and should be swallowed whole with water. Treatment initiates with a titration pack that lasts for 5 days, the patient's prescribed maintenance dose of siponimod is reached on day 6. During the first 6 days of treatment, if a titration dose is missed on one day treatment needs to be re initiated with a new titration pack. If a dose is missed after day 6, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled. If maintenance treatment is interrupted for ≥4 consecutive daily doses, siponimod needs to be re initiated with a new titration pack. Siponimod should be used with caution in patients aged ≥ 65 years due to insufficient data on safety and efficacy. No dose adjustment is needed in patients with renal impairment. Siponimod must not be used in patients with severe hepatic impairment (Child Pugh class C). Caution should be exercised when initiating treatment in patients with mild or moderate hepatic impairment, no dose adjustment is needed. **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. **Warnings/Precautions:** Siponimod is not recommended in patients with: Severe cardiac arrhythmias requiring Class Ia (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic drugs, calcium channel blockers (e.g. verapamil, diltiazem) and other medications (e.g. ivabradine or digoxin) which are known to decrease the heart rate (HR). A history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension, or severe untreated sleep apnoea. QTc prolongation >500 msec. *Infections:* Siponimod reduces the peripheral lymphocyte count to 20-30% of baseline and may increase the risk of infections. Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are recommended periodically during treatment. Confirmed absolute lymphocyte counts <0.2 x 10^9/l, leads to dose reduction to 1 mg, or interruption of supply in patients already receiving 1 mg. A case of cryptococcal meningitis (CM) has been reported for siponimod. Siponimod should be suspended in patients with symptoms consistent with CM until CM has been excluded. Initiate appropriate treatment if CM is diagnosed. No cases of progressive multifocal leukoencephalopathy (PML) have been reported. Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML, if suspected, treatment should be suspended. Cases of herpes viral infection have been reported in the development programme. Patients without a physician confirmed history of varicella zoster virus (VZV) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before starting siponimod. A full course of vaccination with varicella vaccine is recommended for antibody negative patients prior to commencing treatment. Initiation of treatment should be postponed for 1 month to allow 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. The possible return of disease activity should be considered when stopping siponimod. Anti neoplastic, immune modulating or immunosuppressive therapies should be co administered with caution due to the risk of additive immune system effects. *Macular oedema:* Macular oedema was more frequently reported with siponimod than with placebo in the clinical study. An ophthalmological evaluation is recommended 3 4 months after treatment initiation. Patients should report visual disturbances while on siponimod and an evaluation of the fundus, including the macula, is recommended. Siponimod should not be initiated in patients with macular oedema until resolution. Caution should be used in patients with a history of diabetes mellitus, uveitis or underlying/co existing retinal disease due to a potential increase in risk of macular oedema. Ophthalmological evaluation prior to initiating therapy and regularly while receiving siponimod therapy is recommended for these patients. Siponimod should be discontinued if a patient develops macular oedema. *Bradyarrhythmia:* Initiation of siponimod results in a transient decrease in HR, and a titration scheme to reach the maintenance dose on day 6 is applied at the start of treatment. HR decrease starts within one hour of first dose and the day 1 decline is maximal at approximately 3 to 4 hours (average 5 to 6 bpm). Further HR decreases upon up-titration are seen, with maximal decrease reached on day 5 to 6. With continued dosing HR starts increasing after day 6 and reaches placebo levels within 10 days after initiation. HR below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic. The decrease in HR induced by siponimod can be reversed by parenteral doses of atropine or isoprenaline. Treatment initiation has been associated with transient atrioventricular conduction delays manifesting in most cases as first degree atrioventricular (AV) blocks. Second degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at treatment initiation in >1.7% of patients in clinical studies. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours and did not require discontinuation of siponimod. Patients with the following cardiac conditions should be observed for 6 hours after the first dose of siponimod for signs and symptoms of bradycardia: sinus bradycardia (HR <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. If post dose bradyarrhythmia or conduction related symptoms occur or if ECG 6 hours post dose shows new onset second degree or higher AV block or QTc ≥500 msec, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If pharmacological treatment is required, monitoring should be continued overnight and 6 hour monitoring should be repeated after the second dose. If siponimod is considered in patients with pre existing significant QT prolongation or who are already being treated with QT prolonging medicinal products with known arrhythmogenic properties, advice from a cardiologist should be sought prior to initiation in order to determine the most appropriate monitoring strategy during treatment initiation. If concomitant treatment is considered during initiation of siponimod, advice from a cardiologist should be sought regarding the switch to a non heart rate lowering medicinal product or appropriate monitoring for treatment initiation. Bradyarrhythmic effects are more pronounced when siponimod is added to beta blocker therapy. For patients receiving a stable dose of beta blocker, the resting HR should be considered before introducing treatment (>50 bpm siponimod can be introduced, if resting HR is ≤50 bpm, then beta blocker treatment should be interrupted until the baseline HR is >50 bpm). Following siponimod initiation treatment with beta blocker can be re initiated after up titration to maintenance dose. *Liver function:* Recent (i.e. within last 6 months) cm is transaminase and bilirubin levels should be available before initiating siponimod. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked. Discontinue siponimod if significant liver injury is confirmed. Caution should be exercised in patients with a history of significant liver disease. *Cutaneous neoplasms:* In clinical studies, basal cell carcinoma was the most common neoplasm reported with a similiar incidence in the siponimod 2 mg and placebo groups. Other skin malignancies, including melanoma, have been reported in patients treated with siponimod and in patients on long term therapy with another S1P modulator. 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:* Rare cases of posterior reversible encephalopathy syndrome have been reported for another S1P modulator but not for siponimod. Should a patient on siponimod 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:* When switching from other disease modifying therapies, the half life and mode of action of the other therapy must be considered. A CBC is recommended prior to initiating siponimod to ensure that immune effects of the previous therapy have resolved. Initiating siponimod after alemtuzumab is not recommended due to the characteristics and duration of alemtuzumab immune suppressive effects. Siponimod can generally be started immediately after discontinuation of beta interferon or glatiramer acetate. *Blood pressure effects:* Special care is indicated if patients with uncontrolled hypertension are treated with siponimod. Hypertension was more frequently reported in patients on siponimod than placebo in the clinical study. Blood pressure should be regularly monitored during treatment. *Women of childbearing potential:* Before initiation of treatment, women of childbearing potential must be informed of the risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after treatment discontinuation. *Stopping therapy:* Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. Siponimod remains in the blood for up to 10 days after discontinuation and the possibility of severe exacerbation of disease after stopping siponimod should be considered. In 90% of SPMS patients, lymphocyte counts return to the normal range within 10 days of stopping therapy. Residual pharmacodynamic effects may persist for up to 3 4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system and therefore caution should be exercised for 3 to 4 weeks after the last dose. *Interference with haematological testing:* Siponimod reduces blood lymphocyte counts, therefore peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a treated patient. **Interactions:** Caution should be exercised during concomitant administration with antineoplastic, immune modulating or immunosuppressive therapies, and in the weeks after administration of any of these medicinal products is stopped, due to the risk of additive immune effects. Due to additive effects on heart rate siponimod should not be concomitantly used in patients receiving class Ia or class III anti arrhythmic medicinal products, QT prolonging medicinal products with known arrhythmogenic properties, heart rate lowering calcium channel blockers or other substances that may decrease heart rate. Vaccinations may be less effective during and for up to 4 weeks after treatment. Avoid use of live attenuated vaccines due to infection risk. Siponimod is metabolised primarily by cytochrome P450 2C9 (CYP2C9) (79.3%) and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%). Concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended due to a significant increase in siponimod exposure. Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. Due to an expected reduction in siponimod exposure, the appropriateness and possible benefit of the treatment should be considered when siponimod is combined with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype, and with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype. No interaction has been observed with ethinylestradiol and levonorgestrel oral contraceptives when co-administered with siponimod. **Fertility, pregnancy and lactation:** Siponimod is contraindicated in women of childbearing potential not using effective contraception. Siponimod should not be used during breast feeding. The effect of siponimod on human fertility has not been evaluated. **Driving and using machines:** Siponimod has no or negligible influence on the ability to drive and use machines. Dizziness may occasionally occur when initiating therapy, therefore patients should not drive or use machines during the first day of treatment. **Undesirable effects:** Very common (≥1/10): headache, hypertension, liver function test increased. Common (≥1/100 to <1/10): herpes zoster, melanocytic naevus, lymphopenia, dizziness, seizure, tremor, macular oedema, bradycardia, atrioventricular block (first and second degree), nausea, diarrhoea, pain in extremity, oedema peripheral, asthenia, pulmonary function test decreased. *Other Adverse Effects:* Please consult the SmPC for a detailed listing of all adverse events. **Legal classification:** POM **Marketing Authorisation (MA) number, quantities and price:** EU/1/19/1414/001 Titration pack of Mayzent 0.25 mg containing 12 film coated tablets in PA/alu/PVC/alu blister in wallet: £293.52; EU/1/19/1414/002 Pack of Mayzent 0.25 mg containing 120 film coated tablets in PA/alu/PVC/alu blisters: £1761.12; EU/1/19/1414/003 Pack of Mayzent 2 mg containing 28 film coated tablets in PA/alu/PVC/alu blisters: £1643.72. **Date of last revision of prescribing information:** January 2020 **Full Prescribing Information available from:** Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Tel: (01276) 692255.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.UK/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

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