▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – MAYZENT (SIPONIMOD) TABLETS

1 NAME OF THE MEDICINE

The active ingredient of Mayzent is siponimod.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.25 mg, 1 mg or 2 mg siponimod (as siponimod hemifumarate).

Excipients with a known effect: sugars as lactose (0.25 mg and 1 mg tablet) and lactose (2 mg tablet). For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Mayzent 0.25 mg: Pale red, round, biconvex, beveled-edged film-coated tablet with Novartis logo on one side and T on other side.

Mayzent 1 mg: Violet white, round, biconvex, beveled-edged film-coated tablet with Novartis logo on one side and L on other side.

Mayzent 2 mg: Pale yellow, round, biconvex, beveled-edged film-coated tablet with Novartis logo on one side and II on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

Patient selection

Before initiation of treatment with Mayzent the CYP2C9 genotype of the patient should be determined. Mayzent is contraindicated in patients with a CYP2C9*3*3 genotype (see sections 4.3 Contraindications, 4.4 Special warnings and precautions for use: Pharmacogenomics and 5.2 Pharmacokinetic properties: Pharmacogenomics).

For recommendations related to switching treatment from other disease modifying therapies to Mayzent, see section 4.4 Special warnings and precautions - Prior treatment with immunosuppressive or immune-modulating therapies.

Treatment initiation

Treatment has to be initiated with a titration pack that lasts for 5 days (see section 5 Pharmacological properties). The dose titration starts with 0.25 mg once daily on day 1 and 2, followed by once daily doses of 0.5 mg on day 3 (two tablets of 0.25 mg), 0.75 mg on day 4 (three tablets of 0.25 mg), and 1.25 mg on day 5 (five tablets of 0.25 mg), to reach the maintenance dose of 2 mg* Mayzent starting on day 6.

Table 1 Dose titration regimen to reach Mayzent maintenance dosage

Titration	Titration dose	Titration regimen	Pack
Day 1	0.25 mg	1 x 0.25 mg	TITRATION
Day 2	0.25 mg	1 x 0.25 mg	
Day 3	0.5 mg	2 x 0.25 mg	
Day 4	0.75 mg	3 x 0.25 mg	
Day 5	1.25 mg	5 x 0.25 mg	
Day 6	2 mg	1 x 2 mg	MAINTENANCE

*The recommended maintenance dose is 1 mg daily for patients with CYP2C9 *2*3 or *1*3 genotype. See " below.

During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food.

If a titration dose is missed on one day during the first 6 days of treatment, treatment needs to be re-initiated with a new titration pack.

General target population

The recommended maintenance dose of Mayzent is 2 mg taken once daily with or without food. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily (see Special populations – Pharmacogenomics). For treatment initiation in these patients the same titration pack should be used (see Treatment initiation).

Re-initiation of maintenance therapy after treatment interruption

If Mayzent maintenance treatment is interrupted for 4 or more consecutive daily doses, treatment has to be re-initiated with a new titration pack (see Treatment initiation above). Treatment interruptions for up to 3 missed consecutive daily doses do not require re-titration and treatment should be continued at the maintenance dose level.

Special populations

Pharmacogenomics

Mayzent is contraindicated in patients with a CYP2C9*3*3 genotype (see sections 4.3 Contraindications, 4.4 Special warnings and precautions for use: Pharmacogenomics and 5.2 Pharmacokinetic properties: Pharmacogenomics).

The recommended maintenance dose of Mayzent in patients with a CYP2C9 *2*3 or *1*3 genotype is 1 mg once daily (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties: Pharmacogenomics).

Renal impairment

No Mayzent dose adjustments are needed in patients with renal impairment (see section 4.4 Special warnings and precautions).

Hepatic impairment

No Mayzent dose adjustments are needed in patients with hepatic impairment (see section 4.4 Special warnings and precautions).

Paediatric patients (below 18 years)

No studies have been performed in paediatric patients.

Geriatric patients (65 years or above)

No Mayzent dose adjustment is needed in patients aged 65 years and over.

Method of administration

Mayzent tablets should be taken orally with or without food and swallowed whole with water.

4.3 CONTRAINDICATIONS

Mayzent should not be administered to patients:

- With known hypersensitivity to siponimod or any of the excipients. With a CYP2C9*3/*3 genotype (see section 4.4 Special warnings and precautions for use: Pharmacogenomics).
- Who in the last 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure.
- With second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not have a pacemaker (see section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections

A core pharmacodynamic effect of Mayzent is a dose dependent reduction of peripheral lymphocyte count to 20 to 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5 Pharmacological properties).

The immune system effects of Mayzent may increase the risk of infections (see section 5 Pharmacological properties).

Before initiating treatment with Mayzent, a recent complete blood count (CBC) (i.e. within last 6 months or after discontinuation of prior therapy) should be available.

Initiation of treatment with Mayzent should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of Mayzent, vigilance for infection should be continued throughout this period (see below: Stopping Mayzent therapy).

Patients receiving Mayzent should be instructed to report symptoms of infections to their physician. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with Mayzent, should be considered if a patient develops a serious infection.

Cases of cryptococcal meningitis (CM) have been reported with Mayzent. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with such symptoms and signs should undergo prompt diagnostic evaluation. Mayzent treatment should be suspended until CM has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported for S1P receptor modulators, including Mayzent, and other therapies for MS (see section 4.8 Adverse Effects (undesirable effects)). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, Mayzent treatment should be suspended until PML has been excluded.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptor modulators, including Mayzent, who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by varicella zoster virus (VZV), have been reported with Mayzent. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella zoster virus should be tested for antibodies to VZV before initiating Mayzent (see subsection Vaccination).

Anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects during such therapy (see section 4.5 Interactions with other medicines).

Vaccination

A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Mayzent, following which initiation of treatment with Mayzent should be postponed for 1 month to allow the full effect of vaccination to occur (see section 4.8 Adverse effects).

Live attenuated vaccines

The use of live attenuated vaccines should be avoided while patients are taking Mayzent. Mayzent treatment discontinuation is recommended 1 week prior to vaccination until 4 weeks after vaccination (see section 4.5 Interactions with other medicines and other forms of interactions).

Non-live attenuated vaccines

Non-live attenuated vaccines may be less effective if administered during Mayzent treatment. The decision whether to continue or pause the treatment with Mayzent should be based on the benefit-risk assessment of the individual patient (see below "Stopping Mayzent therapy" and section 4.5 Interactions with other medicines and other forms of interactions).

Macular oedema

Macular oedema (see section 4.8 Adverse effects) with or without visual symptoms was more frequently reported on siponimod (1.8%) than on placebo (0.2%) in the phase 3 clinical study. The majority of cases occurred within the first 3 to 4 months of therapy. 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.

Patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal diseases are at increased risk of macular oedema. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus, uveitis or a history of retinal disorders should have follow-up evaluations while receiving Mayzent therapy.

Continuation of Mayzent therapy in patients with macular oedema has not been evaluated. A decision on whether or not Mayzent should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradyarrhythmia

Heart rate

Since initiation of Mayzent treatment results in a transient decrease in heart rate (see section 5 Pharmacological properties), an up-titration scheme to reach the maintenance dose of Mayzent on day 6 is applied at treatment start (see section 4.2 Dose and method of administration).

After the first titration dose, the heart rate decrease starts within an hour and the day 1 decline is maximal at approximately 3 to 4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days with maximal decrease from day 1-baseline reached on day 5 to 6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on day 1 with the pulse declining on average 5 to 6 beats per minute (bpm). Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after day 6 and reaches placebo levels within 10 days after treatment initiation.

Heart rates below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced mild to moderate symptoms including dizziness or fatigue which resolved within 24 hours without intervention (see section 4.8 Adverse effects).

Atrioventricular Conduction

Initiation of Mayzent treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The atrioventricular conduction delays manifested in most of the cases as first-degree atrioventricular (AV) blocks (prolonged PR interval on electrocardiogram). Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed in less than 1.7% of patients in clinical trials at the time of treatment initiation with Mayzent. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours and did not require discontinuation of Mayzent treatment.

Treatment initiation recommendations

Mayzent treatment initiation with a dose titration is usually well tolerated (see sections 4.2 Dose and method of administration and 4.3 Contraindications).

As a precautionary measure, patients with:

- sinus bradycardia (heart rate (HR) <55 bpm),
- first or second-degree [Mobitz type I] atrioventricular block (AV block),
- or a history of myocardial infarction or heart failure, if not contraindicated

should be observed for a period of 6 hours after the first dose of Mayzent for signs and symptoms of bradycardia. Obtaining an electrocardiogram (ECG) prior to dosing, and at the end of the observation period is recommended in these patients. Should post-dose bradyarrhythmia or conduction related symptoms occur or if ECG 6 hours post-dose show new onset second degree or higher AV block or QTc ≥500 msec, appropriate management should be initiated and observation should be 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.

Due to the risk of serious cardiac rhythm disturbances, Mayzent should not be used in patients with sino-atrial heart block.

Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest with onset > 6 months prior to Mayzent treatment initiation, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea, Mayzent should not be used in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

Use of Mayzent in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

A thorough QT study demonstrated no significant direct QT prolonging effect of Mayzent and Mayzent is not associated with an arrhythmogenic potential related to QT prolongation. Initiation of Mayzent treatment may result in decreased heart rate and indirect prolongation of the QT interval during the titration phase. Mayzent was not studied in patients with significant QT prolongation (QTc >500 msec) or who were treated with QT prolonging drugs. If treatment with Mayzent is considered in patients with pre-existing significant QT prolongation or who are treated with QT prolonging drugs with known arrhythmogenic properties, advice from a

cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy during treatment initiation.

Mayzent has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-arrhythmic drugs (e.g. amiodarone, sotalol). Class Ia and Class III anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of Mayzent treatment results in decreased heart rate, Mayzent should not be used concomitantly with these drugs during treatment initiation.

Experience with Mayzent is limited in patients receiving concurrent therapy with heart-rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. ivabradine or digoxin). Concomitant use of these substances during Mayzent initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Mayzent should generally not be initiated in patients who are concurrently treated with these substances.

If concomitant treatment with Mayzent and the above mentioned substances is considered during initiation of treatment with Mayzent, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

Bradyarrhythmic effects are more pronounced when Mayzent is added to beta-blocker therapy. For patients receiving a stable dose of beta-blocker, the resting heart rate should be considered before introducing Mayzent treatment. If the resting heart rate is >50 bpm under chronic beta-blocker treatment, Mayzent can be introduced. If resting heart rate is ≤50 bpm, then beta-blocker treatment should be interrupted until the baseline heart-rate is >50 bpm. Treatment with Mayzent can then be initiated and treatment with beta-blocker can be re-initiated after Mayzent has been up-titrated to the target maintenance dose.

Missed dose during treatment initiation and re-initiation of therapy following treatment interruption

If a titration dose is missed on one day during 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 (see above "Treatment initiation recommendations" and section 4.2 Dose and method of administration).

Liver function

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Mayzent. In study A2304, Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times upper limit of normal (ULN) were observed in 5.6% of patients treated with Mayzent 2 mg compared to 1.5% of patients receiving placebo (see section 4.8 Adverse effects). In clinical trials, Mayzent was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic function.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia or jaundice and/or dark urine during treatment, should have liver enzymes checked and Mayzent should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test (LFT) values when taking Mayzent,

caution should be exercised when using Mayzent in patients with a history of significant liver disease.

Cutaneous neoplasms

In study A2304, the incidence of basal cell carcinoma (BCC) was 1.1% in Mayzent-treated patients and 1.3 % in patients receiving placebo. For squamous cell carcinoma (SCC) the incidence in study A2304 was the same for Mayzent-treated patients and placebo (0.2%). However, additional cases of BCC and SCC in Mayzent-treated patients have been reported with longer exposure (see section 4.8 Adverse Effects). Cases of other skin malignancies, including melanoma, have also been reported in patients treated with Mayzent and in patients treated with other S1P receptor modulators (see section 4.8 Adverse Effects).

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer and patients with suspicious skin lesions. Patients should be advised to report any suspicious skin lesions to their physician for prompt evaluation. Patients treated with Mayzent should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy.

Blood pressure effect

Hypertension was more frequently reported in patients on siponimod (12.6%) than on placebo (9.0%) in the phase 3 clinical trial in patients with SPMS. Treatment with siponimod resulted in an increase of systolic and diastolic blood pressure starting early after treatment initiation, reaching maximum effect after approximately 6 months of treatment (systolic 3 mmHg, diastolic 1.2 mmHg) and staying stable thereafter. The effect persisted with continued treatment. Blood pressure should be monitored during treatment with Mayzent and managed appropriately.

Unexpected neurological or psychiatric symptoms/signs

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported for another sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for Mayzent in the development program. However, should a patient on Mayzent treatment develop any unexpected neurological or psychiatric symptoms/signs (e.g. cognitive deficits, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs or any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider a magnetic resonance imaging (MRI).

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 to avoid an additive immune effect whilst at the same time minimizing risk of disease reactivation.

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with Mayzent after alemtuzumab is not recommended unless the benefits of Mayzent treatment clearly outweigh the risks for the individual patient.

Pharmacogenomics

Before initiation of treatment with Mayzent, patients should be genotyped (as tested and confirmed by NATA/RCPA accredited Pathology Lab) for CYP2C9 to determine the CYP2C9 genotype (see section 4.2 Dose and method of administration, 4.3 Contraindications and 5.2 Pharmacokinetic properties: Pharmacogenomics).

Stopping Mayzent 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 should be considered after stopping siponimod treatment. 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 stopping Mayzent therapy in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS) (see section 4.4 Special warnings and precautions for use – Infections).

After stopping Mayzent therapy siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts typically return to the normal range in the vast majority (90%) of SPMS patients within 10 days of stopping therapy. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count may persist for up to 3 to 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 applied 3 to 4 weeks after the last dose.

Use in patients with asthma

In the phase 3 clinical study in patients with SPMS, mean reductions from baseline in FEV_1 in the siponimod group were 0.1 L with no change in the placebo group (see "Respiratory Effects" in section 4.8 Adverse Effects). These reductions were greater (approximately 0.15 L mean change from baseline in FEV_1) in patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease (COPD) treated with siponimod. Mayzent may be used with caution in patients with asthma. However, asthma status should be reviewed and medications (including preventers) should be optimised before Mayzent treatment is considered.

Use in hepatic impairment

No dose adjustments for siponimod are needed in patients with hepatic impairment. The unbound siponimod pharmacokinetics AUC is 15% and 50% higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg single dose studied. The mean half-life of siponimod was unchanged in hepatic impairment.

Use in renal impairment

No siponimod dose adjustments are needed in patients with mild, moderate or severe renal impairment. Mean siponimod half-life and C_{max} (total and unbound) were comparable between subject with severe renal impairment and healthy subjects. Total and unbound AUCs were only slightly increased (by 23 to 33%), compared to healthy subjects. The effects of end-stage renal disease or hemodialysis on the pharmacokinetics of siponimod has not been studied. Due to the high plasma protein binding (>99.9%) of siponimod, hemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations.

Use in the elderly

Results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, to date clinical experience in patients aged above 65 years is limited.

Paediatric use

No studies have been performed in paediatric patients.

Effects on laboratory tests

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 Mayzent.

Laboratory tests requiring the use of circulating mononuclear cells require large blood volumes due to reduction in the number of circulating lymphocytes.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic interactions

Anti-neoplastic, immune-modulating or immunosuppressive therapies

Mayzent has not been studied in combination with anti-neoplastic, immune-modulating or immunosuppressive therapies. Caution should be used during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks following stopping administration of any of these drugs (see section 4.4 Special warnings and precautions).

When switching from other disease modifying therapies, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing risk of disease reactivation.

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with Mayzent after alemtuzumab is not recommended unless the benefits of Mayzent treatment clearly outweigh the risks for the individual patient.

Mayzent can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate

During treatment initiation Mayzent should not be concomitantly used in patients receiving Class Ia (e.g. quinidine, procainamide), Class III anti-arrhythmic drugs (e.g. amiodarone, sotalol), QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (such as verapamil or diltiazem) or other substances which may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate. If treatment with Mayzent is considered, advice from a cardiologist should be sought (see section 4.4 Special warnings and precautions - Treatment initiation recommendations).

Beta-blockers

Caution should be applied when Mayzent is initiated in patients receiving beta-blockers due to the additive effects on lowering heart rate (see section 4.4 Special warnings and precautions -

Treatment initiation recommendations). Beta-blocker treatment can be initiated in patients receiving stable doses of Mayzent.

The negative chronotropic effect of co-administration of siponimod and propranolol was evaluated in a dedicated PD/safety study. The addition of propranolol on top of siponimod PK/PD steady-state had less pronounced negative chronotropic effects (less than additive) in comparison to addition of siponimod on top of propranolol PK/PD steady state (additive HR effect).

Vaccination

Live attenuated vaccines

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during Mayzent treatment. Mayzent treatment discontinuation is recommended 1 week prior to vaccination until 4 weeks after vaccination (see section 4.4 Special warnings and precautions for use - Vaccination).

Non-live attenuated vaccines

Potential effects of siponimod on the immune response/immunogenicity of selected non-live attenuated vaccines were investigated in a dedicated study with two representative vaccines, a PPV-23 vaccine (T cell-independent vaccine) and a quadrivalent influenza vaccine (T cell-dependent vaccine). The study demonstrated that concomitant Mayzent treatment does not compromise the efficacy of a PPV-23 vaccination and therefore no Mayzent treatment pause is necessary. The efficacy of the influenza vaccination is not compromised if Mayzent treatment is paused 1 week prior and until 4 weeks after vaccination. Shorter treatment pause from 10 days prior to 14 days after vaccination and concomitant Mayzent treatment showed only modest impact on influenza vaccination efficacy with responder rates approximately 15% to 30% lower than on placebo (see section 4.4 Special warnings and precautions for use - Vaccination).

Pharmacokinetic interactions

Potential of other drugs to affect siponimod pharmacokinetics (PK) (siponimod as a substrate)

Siponimod is primarily metabolized by cytochrome P450CYP2C9 (79.3%) and to a lesser extent by CYP3A4 (18.5%). CYP2C9 is a polymorphic enzyme and the drug-drug interaction (DDI) effect in presence of CYP3A or CYP2C9 perpetrator drugs is predicted to be dependent on the CYP2C9 genotype (see section 5.2 Pharmacokinetic properties: Pharmacogenomics).

CYP2C9 and CYP3A4 inhibitors

Caution should be applied with concomitant use of Mayzent with drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition due to a clinically relevant increase in exposure to siponimod. This concomitant drug regimen can consist of moderate CYP2C9/CYP3A4 dual inhibitors (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor.

Moderate CYP2C9/CYP3A4 dual inhibitors (e.g. fluconazole) are expected to increase siponimod exposure by 1.78 to 2.73-fold according to clinical drug-drug interaction studies

and in silico (physiologically based pharmacokinetics) evaluation of the drug interaction potential.

CYP2C9 and CYP3A4 inducers

Caution should be applied with concomitant use of Mayzent with drugs that cause moderate CYP2C9 and strong CYP3A4 induction as this may result in a clinically relevant decrease in siponimod exposure and potential loss of efficacy.

This includes dual moderate CYP2C9/strong CYP3A4 inducers (e.g. rifampicin or carbamazepine) or a combination of a moderate CYP2C9 inducer with a separate strong CYP3A4 inducer, in all CYP2C9 genotypes. Patients should be monitored for reduced therapeutic effect.

Strong CYP3A4 and moderate CYP2C9 induction has been shown to significantly reduce siponimod exposure. Clinical drug–drug interaction studies and PBPK modelling predict a reduction in exposure by up to 65% with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine or rifampicin), and up to 20% with moderate CYP3A4 inducers (e.g. modafinil).

Caution is also needed with concomitant use of Mayzent with moderate CYP3A4 inducers (e.g. efavirenz, modafinil) for patients with CYP2C9*1*3 or *2*3 genotypes.

Potential of siponimod to affect the PK or PD of other drugs

Oral contraceptives

Co-administration with siponimod did not reveal clinically relevant effects on the PK and PD 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing siponimod to be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Mayzent and for at least ten days after stopping treatment with Mayzent (see section 4.4 Special warnings and precautions for use – Stopping Mayzent therapy).

Fertility

There are no data with Mayzent on fertility in humans.

Siponimod had no effect on male reproductive organs in rats and monkeys or fertility parameters in rats.

In fertility studies in male and female rats, animals received oral doses of siponimod up to 200 mg/kg/day and 1 mg/kg/day respectively, before mating and until 2 weeks post mating for male, and until gestation day 6 for females.

There was no effect on mating or sperm parameters in males and on mating and early embryonal development until implantation in female rats, indicating that siponimod is not associated with an increased risk of effect on fertility.

Changes in reproductive organs were only seen in rats exposed to high levels of siponimod.

Use in pregnancy – Pregnancy Category D

Risk summary

There are no available data on Mayzent use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Based on animal data and its mechanism of action Mayzent can cause fetal harm when administered to a pregnant woman. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod at levels similar to those in humans at the highest recommended dose of 2 mg/day.

Pregnant women should be advised of a potential risk to the fetus if Mayzent is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

The use of Mayzent in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to the fetus.

Epidemiologic studies from USA, Canada, major EU countries and South American countries have shown that the risk of birth defects in MS population is similar to that in the general population. For spontaneous abortions and stillbirths, the background risk in the MS population in the US appears to be similar to that in the general US population.

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of siponimod up to 40 mg/kg/day and 5 mg/kg/day, respectively, during the period of organogenesis. A significant increase in embryo-fetal mortality occurred at dose levels that did not produce maternal toxicity.

In rats, fetal resorption and teratogenicity (skeletal malformations, e.g. cleft palate and misshapen clavicles, cardiomegaly and edema) were noted at ≥1 mg/kg/day. No maternal reproductive and fetal no observed adverse effects levels (NOAELs) were established. At 1 mg/kg/day (lowest observed adverse effect level) the maternal exposure (area under the curve, AUC) was approximately 19 times the exposure in humans at the highest recommended dose (2 mg).

In rabbits, siponimod resulted in a significant increase in embryo-fetal deaths and skeletal variations at doses ≥1 mg/kg/day, and abortions and increased skeletal or visceral variations at 5 mg/kg/day. The maternal reproductive NOAEL was 1 mg/kg/day and the NOAEL for embryo-fetal development was 0.1 mg/kg/day. At 0.1 mg/kg/day (NOAEL), the maternal exposure (AUC) was estimated to be approximately 0.2 times the exposure in humans at the highest recommended dose (2 mg).

In a pre- and post-natal development study in rats, pregnant animals received oral doses of siponimod up to 0.5 mg/kg/day during the period of organogenesis and until weaning. In the F0 generation dams, ≥0.15 mg/kg/day resulted in effects on body weight and food consumption as well as an increased gestation length. At 0.5 mg/kg/day, the numbers of dead and malformed pups were increased.

In F1 generation pups, adverse clinical signs, decreased body weights and decreased postnatal survival were observed at ≥0.15 mg/kg/day. Increased abnormalities including external, urogenital and skeletal findings were observed at ≥0.15 mg/kg/day. In F1 generation adults, delayed sexual maturation, but no effects on reproductive function or behavioral performance, were noted at 0.5 mg/kg/day. At 0.05 mg/kg/day (NOAEL) in rat, the maternal exposure (AUC) was approximately 0.9 times the exposure in humans at the highest recommended dose (2 mg).

Malformations and/or embryofetal mortality identified in rat and rabbit reproductive and developmental studies may be related to the modulation of the S1P receptor. The receptor affected by siponimod is known to be involved in vascular formation and skeletal development during embryogenesis in rodents.

Use in lactation.

Risk summary

It is not known if siponimod is present in human milk. There are no data on the effects of siponimod on the breast-fed child or on milk production.

Since many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Mayzent, a nursing woman should be advised on the potential risks to the child. Women receiving Mayzent should not breast-feed.

Animal data

In lactating rats dosed with a single oral dose of 10 mg/kg, siponimod and its metabolites passed into the milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

A total of 1,737 multiple sclerosis (MS) patients have been treated with siponimod in doses of at least 2 mg daily. These were included in study A2304, a phase 3, multicenter, randomized, double-blind, placebo-controlled study in patients with SPMS and study A2201, a phase 2, double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled study in

patients with relapsing-remitting MS (RRMS). Study A2304 randomized 1,651 SPMS patients 2:1 to receive either Mayzent 2 mg once daily or placebo. Median treatment duration was 18 months (range 0 to 37 months). Study A2201 randomized a total of 297 RRMS patients to receive Mayzent at once daily doses ranging from 0.25 mg to 10 mg or placebo for up to 6 months.

In study A2304 a higher percentage of siponimod than placebo patients completed the double-blinded part of the study drug treatment (66.7% and 59.0%, respectively). The most common reasons for discontinuations in the siponimod and placebo groups were subject/guardian decisions (10.3% siponimod vs. 13.0% placebo), disease progression (9.1% for siponimod vs. 14.8% for placebo) and adverse events (8.5% siponimod vs 5.1% placebo). The most common adverse drug reactions in the siponimod 2 mg group (incidence ≥10%) in study A2304 were headache and hypertension.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials have been defined primarily on the basis of the experience in study A2304 (Table 2) and are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2: Percentage of patients with adverse drug reactions in study A2304^

Adverse drug reactions	Mayzent (Siponimod) 2 mg N= 1099 %	Placebo N=546 %	Frequency category
Infections and infestations			
Herpes zoster*	2.5	0.7	common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Melanocytic naevus*	4.9	2.9	common
Basal cell carcinoma**	1.1	1.3	common
Squamous cell carcinoma**	0.2	0.2	uncommon
Malignant melanoma	0.2	0.0	uncommon
Blood and lymphatic system disorders			
Lymphopenia*	1.3	0.0	common
Nervous system disorders			

Adverse drug reactions	Mayzent (Siponimod) 2 mg N= 1099 %	Placebo N=546 %	Frequency category
Headache*	15.2	13.9	very common
Dizziness	6.8	4.8	common
Seizure*	1.7	0.4	common
Tremor*	1.6	0.5	common
Eye disorders			
Macular oedema*	1.8	0.2	common
Cardiac disorders			
Bradycardia*	6.2	3.1	common
Atrioventricular block*(1st & 2nd degree)	1.6	0.7	common
Vascular disorders			
Hypertension*	12.6	9.0	very common
Gastrointestinal disorders			
Nausea	6.7	3.5	common
Diarrhoea	6.4	4.2	common
Musculoskeletal and connective tissue disorders			
Pain in extremity*	6.3	4.0	common
General disorders and administration site conditions			
Oedema peripheral*	8.1	4.4	common
Asthenia	2.5	1.3	common
Investigations			
Liver function test increased*	11.3	3.1	very common
Pulmonary function test decreased*	1.5	0.5	common

^Core phase - Controlled pool

Adverse drug reactions	Mayzent (Siponimod) 2 mg N= 1099 %	Placebo N=546 %	Frequency category

**Grouping of preferred terms (PTs) were considered for ADR frequency determination*

***Adverse drug reactions from open-label extension part of the phase 3 study A2304*

Adverse drug reactions from open-label extension part of clinical trials or from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Mayzent via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions from open-label extension part of clinical trials or from spontaneous reports and literature (frequency not known)

Infections and infestations
Progressive multifocal leukoencephalopathy; cryptococcal meningitis; herpes viral infection including cases of meningitis or meningoencephalitis caused by varicella zoster virus (see section 4.4 Special warnings and precautions for use).
Immune system disorders
Hypersensitivity reactions including rash, urticaria and angioedema.

Description of selected adverse drug reactions

Infections

In the phase 3 clinical trial in patients with SPMS the overall rate of infections was comparable between the patients on siponimod and those on placebo (49.0% vs. 49.1% respectively). However, an increase in the rate of herpes zoster infections was reported on siponimod (2.5%) compared to placebo (0.7%).

Macular oedema

Macular oedema was more frequently reported in patients receiving siponimod (1.8%) than placebo (0.2%). Although the majority of cases occurred within 3 to 4 months of commencing siponimod, cases were also reported in patients treated with siponimod for more than 6 to 12 months (see section 4.4 Special warnings and precautions). Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated.

Bradyarrhythmia

Initiation of siponimod treatment results in a transient decrease in heart rate and may also be associated with atrio-ventricular conduction delays (see section 4.4 Special warnings and precautions).

Liver function tests

Increased hepatic enzymes (mostly ALT elevation) have been reported in MS patients treated with siponimod. In the phase 3 trial in patients with SPMS, liver function test increase were more frequently observed in patients on siponimod (11.3%) than in those on placebo (3.1%), mainly due to liver transaminase (ALT/AST/GGT) elevations. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of siponimod (see section 4.4 Special warnings and precautions).

Seizures

Cases of seizures were reported in 1.7% of patients treated with siponimod compared to 0.4% on placebo in the phase 3 clinical trial in patients with SPMS. It is not known whether these events were related to the effects of MS, to siponimod, or to a combination of both.

Respiratory effects

Minor reductions in forced expiratory volume in 1 second (FEV_1) and in the diffusing capacity of the lung for carbon monoxide (DLCO) values were observed with siponimod treatment. At month 3 and month 6 of treatment in the phase 3 clinical trial in patients with SPMS, mean changes from baseline in the siponimod group were -0.1 L at each time point, with no change in the placebo group. On chronic treatment, this reduction did not translate into clinically significant adverse events and was not associated with an increase in reports of cough or dyspnea.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Healthy subjects received siponimod as single doses (0.1 to 75 mg) or as multiple doses (0.25 to 20 mg). The single maximum tolerated dose was determined to be 25 mg based upon the occurrence of symptomatic bradycardia after single doses of 75 mg. The highest investigated multiple dose of 20 mg over 28 days was well tolerated (9 subjects receiving 100 mg on the last day of dosing and 5 subjects receiving up to 200 mg daily for a duration of 3 to 4 days). Some of the 9 subjects had asymptomatic mild to moderate transient elevations of liver function tests.

One patient (with a history of depression) took 84 mg siponimod. Aside from a slight elevation in liver transaminases, the patient did not experience any other adverse events from the overdose.

If the overdose constitutes first exposure to Mayzent or occurs during the dose titration phase of Mayzent it is important to observe for signs and symptoms of bradycardia, which could include overnight monitoring. Regular measurements of pulse rate and blood pressure are

required and electrocardiograms should be performed (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions).

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group, ATC code

Pharmacotherapeutic group: Immunosuppressants, sphingosine-1-phosphate (S1P) receptor modulators, ATC code: L04AE03.

Mechanism of action

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds selectively on two out of five G-protein-coupled receptors (GPCRs) for S1P, namely $S1P_1$ and $S1P_5$. By acting as a functional antagonist on $S1P_1$ receptors on lymphocytes, siponimod prevents egress from lymph nodes. This reduces the recirculation of T-cells into the central nervous system (CNS) to limit central inflammation. Siponimod spares effector memory T-cells in peripheral tissues and blood and does not impair lymphocyte activation.

Siponimod readily crosses the blood brain barrier.

In animal studies direct effects have been demonstrated for siponimod on neural cells, via $S1P_1$ on astrocytes and $S1P_5$ on oligodendrocytes. In a mouse model of experimental autoimmune encephalomyelitis a direct neuroprotective effect, independent from effects on lymphocytes, was also demonstrated for siponimod applied centrally (via intracerebroventricular infusions).

Pharmacodynamics (PD)

Immune system

Mayzent induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, due to the reversible sequestration of lymphocytes in lymphoid tissues.

With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90% CI) lymphocyte count of approximately 0.560 (0.271 to 1.08) cells/nL in a typical CYP2C9*1*1 or *1*2, non-Japanese SPMS patient, corresponding to 20 to 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing.

Lymphocyte counts typically return to the normal range in the vast majority (90%) of SPMS patients within 10 days of stopping therapy. After stopping Mayzent treatment residual lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose.

Cardiac electrophysiology

Heart rate and rhythm

Mayzent causes a transient reduction in heart rate and atrioventricular conduction upon treatment initiation (see section 4.8 Adverse effects). The maximum decline in heart rate is seen in the first 6 hours post-dose. Autonomic responses of the heart, including diurnal

variation of heart rate and response to physical exercise, are not affected by siponimod treatment.

A transient, dose-dependent decrease in heart rate was observed during the initial dosing phase of Mayzent, that plateaued at doses ≥5 mg and bradyarrhythmic events (AV Blocks and sinus pauses) were detected at a higher incidence under Mayzent treatment compared to placebo.

No second degree AV blocks of Mobitz type II or higher degree were observed. Most AV blocks and sinus pauses occurred above the therapeutic dose of 2 mg with notably higher incidence under non titrated conditions compared to dose titration conditions.

The decrease in heart rate induced by Mayzent can be reversed by atropine or isoprenaline.

Potential to prolong the QT interval

The effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of siponimod on cardiac repolarization were investigated in a thorough QT study. The results did not suggest an arrhythmogenic potential related to QT prolongation with siponimod. Siponimod increased the placebo-corrected baseline-adjusted mean QTcF (ΔΔQTcF) by more than 5 ms with a maximum mean effect of 7.8 ms (2 mg) and 7.2 ms (10 mg), respectively at 3 h post-dose. The upper bound of the one-sided 95% CI for the ΔΔQTcF at all time points remained below 10 ms. Categorical analysis revealed no treatment-emergent QTc values above 480 ms, no QTc increases from baseline of more than 60 ms and no corrected or uncorrected QT/QTc value exceeded 500 ms.

Pulmonary function

Mayzent treatment with single doses or multiple doses for 28 days is not associated with clinically relevant increases in airway resistance as measured by forced expiratory volume in 1 second (FEV1) and forced expiratory flow (FEF) during expiration of 25 to 75% of the forced vital capacity (FEF25-75%). A slight trend of reduced FEV1 was detected at non-therapeutic single doses (>10 mg). Multiple doses of Mayzent were associated with mild to moderate changes in FEV1 and FEF25-75% which were not dose and daytime dependent and were not associated with any clinical signs of increased airway resistance.

Concomitant treatment of Mayzent with propranolol resulted in minimal decrease of FEV1 in comparison to propranolol alone. The changes with the individual drugs or with the combination were within the physiological variability of FEV1 and not clinically significant.

Clinical trials

The efficacy of Mayzent was demonstrated in a phase 3 study that evaluated once-daily doses of Mayzent 2 mg in patients with SPMS. A dose-ranging phase 2 study in patients with RRMS demonstrated dose-dependent reduction in inflammatory lesions on MRI and found Mayzent 2 mg to provide a near maximum effect.

Study A2304 (EXPAND) in SPMS

Study A2304 was a randomized, double-blind, placebo-controlled, event and follow-up duration-driven, phase 3 study in patients with SPMS who had documented evidence of progression in the prior 2 years in the absence or independent of relapses, no evidence of relapse in 3 months prior to study enrollment and with Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at study entry.

Patients were randomized 2:1 to receive either once daily Mayzent 2 mg or placebo. Evaluations were performed at screening and every 3 months and at the time of relapse. MRI evaluations were performed at screening and every 12 months.

The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP) determined as at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5 or more) sustained for 3 months. Key secondary endpoints were time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test (T25FW) and change from baseline in T2 lesion volume. Additional secondary endpoints included time to 6-month CDP, percent brain volume change, measures of inflammatory disease activity (annualized relapse rate, MRI lesions). Change in cognitive processing speed on Symbol Digit Modality Test oral score was an exploratory endpoint.

Study duration was variable for individual patients (median study duration was 18 months, range 11 to 37 months).

The study randomized 1,651 patients to either Mayzent 2 mg (N=1,105) or placebo (N=546); 82% of Mayzent-treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, median disease duration was 16.0 years and median EDSS score was 6.0 at baseline; 63.9% of patients had no relapses in the 2 years prior to study entry and 78% had no gadolinium (Gd)-enhancing lesions on their baseline MRI scan; 78.3% of patients had been previously treated with a therapy for their MS.

Time to onset of 3-month confirmed disability progression (primary endpoint) was significantly delayed for Mayzent with a 21.2% risk reduction compared to placebo (hazard ratio (HR) 0.79, p<0.0134).

The results for this study are summarized in Table 4 and Figure 1.

Table 4: Overview of results from efficacy endpoints

Efficacy Parameter	Statistic	Estimate (95% CI)	p-value
Clinical			
Time to 3-month CDP (primary endpoint)	Hazard ratio (1)	0.79 (0.65,0.95)	0.0134
Time to 6-month CDP	Hazard ratio (1)	0.74 (0.60, 0.92)	0.0058
Annualized relapse rate (ARR), confirmed relapses	ARR ratio (3)	0.45 (0.34, 0.59)	<0.0001
Change from baseline in Symbol Digit Modality Test	Treatment difference (4)	1.38 (0.58, 2.18)	0.0007
MRI			
Change from baseline in T2 lesion volume (mm^3)	Treatment difference (2)	-695 (-877, -513)	<0.0001
Percent brain volume change relative to baseline	Treatment difference (2)	0.15 (0.07,0.23)	0.0002

Efficacy Parameter	Statistic	Estimate (95% CI)	p-value
Number of Gd-enhancing T1 weighted lesions	Rate ratio (5)	0.14 (0.10, 0.19)	<0.0001
Number of new/enlarging T2 lesions	Rate ratio (6)	0.19 (0.16, 0.24)	<0.0001

All analyses are based on the full analysis set (FAS), which includes all randomized subjects who took at least one dose of study medication. p values are two-sided.

(1) Hazard ratio (siponimod/placebo), Cox proportional hazard model

(2) Treatment difference in the average over mean changes at Months 12 and 24, repeated measures model

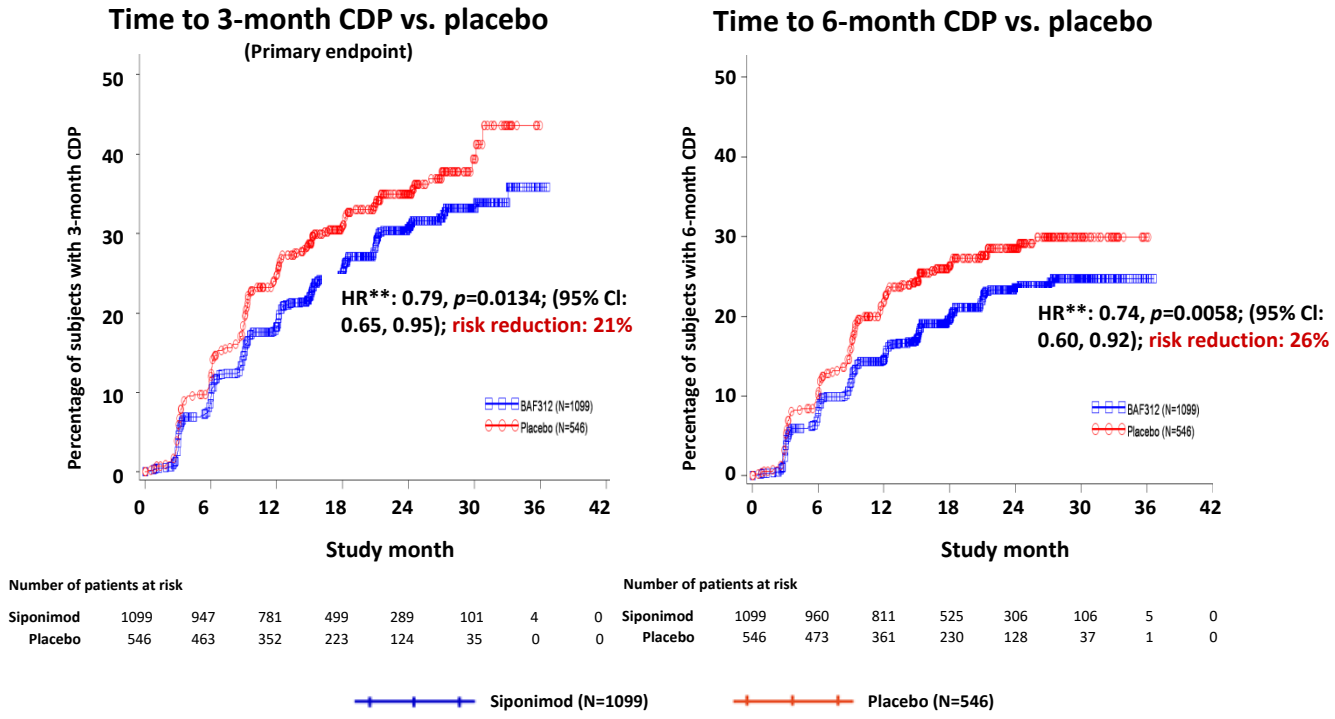
(3) ARR ratio (siponimod/placebo), negative binomial model

(4) Treatment difference in the average over all visits, repeated measures model

(5) Rate ratio (siponimod/placebo) up to and including Month 24, negative binomial model

(6) Rate ratio (siponimod/placebo) per scan, average over Months 12 and 24, negative binomial model

Figure 1: Patients with 3-month and 6-month CDP based on EDSS-Kaplan-Meier curves (FAS)



Mayzent did not significantly delay time to 3-month confirmed ≥20% deterioration in the T25FW compared to placebo (a numerical 6.2% risk reduction was observed).

Results from the study showed a consistent risk reduction in the time to 3-month CDP with Mayzent -compared to placebo in subgroups defined based on gender, age, prior multiple sclerosis therapy, pre-study relapse activity, baseline MRI disease activity and disability levels at baseline.

Study A2201 (BOLD) in RRMS

Study A2201 was a randomized, double-blind, placebo-controlled, adaptive dose-ranging, phase 2 study in patients with RRMS who had experienced at least 2 documented relapses in the past 2 years, or 1 relapse in the past 1 year, or had a positive Gd-enhanced MRI scan at study entry and with an EDSS score of 0 to 5.0.

The primary endpoint of the study was the dose-response relationship among 5 doses of Mayzent and placebo based on the number of combined unique active inflammatory lesions (CUALs) on 3 monthly MRI scans. Other measures included the number of Gd-enhancing lesions and number of new T2 lesions on MRI and MS relapses over 3 and 6 months.

The study randomized 297 patients with RRMS to 2 cohorts to receive once daily Mayzent at doses of 0.5 mg, 2 mg or 10 mg or placebo for up to 6 months in cohort 1 (N=188) and 0.25 mg, 1.25 mg or placebo for up to 3 months in cohort 2 (N=109). MRI evaluations were performed monthly, neurological evaluations every 3 months and at the time of relapse.

Mean age was 36 years, mean disease duration was 7 years; mean number of 2 relapses in the past 2 years and 45% of patients had Gd-enhancing lesions on their baseline MRI scan.

Treatment with Mayzent resulted in a dose-related up to 80% reduction in the number of CUALs compared to placebo (p=0.0001). The model-predicted MRI dose-response curve indicated near-maximal efficacy at 2 mg.

The annualized relapse rate over 6 months was reduced vs placebo by 48% (p=0.148) with 10mg and 66% (p=0.041) with 2 mg; the ARRs were similar for the 0.5 mg and placebo groups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after multiple oral administration of siponimod was about 4 hours (range 2 to 12 hours). Siponimod absorption is extensive (≥70%, based on the amount of radioactivity excreted in urine and the amount of metabolites in feces extrapolated to infinity). The absolute oral bioavailability of siponimod is approximately 84%. For 2 mg siponimod given once daily over 10 days, a mean C_{max} of 30.4 ng/mL and mean AUC_{tau} of 558 h*ng/mL were observed on day 10. Steady state was reached after approximately 6 days of multiple once daily administration of siponimod.

Food effect

Food intake had no effect on the systemic exposure of siponimod (C_{max} and AUC). Therefore Mayzent may be taken without regard to meals (see section 4.2 Dose and method of administration).

Distribution

Siponimod is distributed to body tissues with a moderate mean volume of distribution of 124 L. Siponimod fraction found in plasma is 68% in humans. Animal studies show that siponimod readily crosses the blood-brain-barrier. Protein binding of siponimod is >99.9% in healthy subjects and in hepatic and renal impaired patients.

Metabolism

Siponimod is extensively metabolised, mainly by polymorphic CYP2C9 (79.5%), for the extensive metaboliser CYP2C9*1*1 and its overall contribution to siponimod elimination depends on its genotype and enzyme activity. Residual elimination of siponimod is ascribed to various other cytochromes, including CYP3A4 (6.4%), which are considered to be minor across all CYP2C9 genotypes.

The pharmacological activity of the main metabolites M3 and M17 is not expected to contribute to the clinical effect and the safety of siponimod in humans.

Excretion

An apparent systemic clearance (CL/F) of 3.11 L/h was estimated in MS patients (see below Pharmacogenomics). The apparent elimination half-life is approximately 30 hours.

Siponimod is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion.

Linearity:

Siponimod concentration showed a linear dependence on dose over the range 0.3 mg to 20 mg.

Steady-state-plasma concentrations are reached after approximately 6 days of once daily dosing and steady-state levels are approximately 2 to 3-fold greater than the initial dose. An up-titration regimen is used to stepwise reach the clinical therapeutic dose of siponimod of 2 mg after 6 days and 4 additional days of dosing are required to reach the steady-state-plasma concentrations.

***In vitro* and *in vivo* evaluation of drug interaction potential**

Siponimod (and metabolites M3, M17) as a causative agent of interaction

In vitro investigations indicated that siponimod and its major systemic metabolites M3 and M17 do not show any clinically relevant drug-drug interaction potential at the therapeutic dose of 2 mg once daily for all investigated CYP enzymes and transporters, and do not necessitate clinical investigation.

Co-administration of siponimod with CYP2C9 and CYP3A4 inhibitors

The co-administration of fluconazole (moderate CYP2C9/CYP3A4 dual inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1*1 healthy volunteers led to a two-fold increase in the AUC of siponimod. The co-administration of clarithromycin (strong CYP3A4 inhibitor) 500 mg daily at steady state and a single dose of siponimod 0.25 mg in healthy volunteers with the CYP2C9*1*3 genotype led to a 1.09-fold increase in the AUC of siponimod, which is not clinically relevant.

Drug-drug interaction (DDI) simulations with fluconazole across all CYP2C9 genotypes (excluding CYP2C9*3*3) resulted in exposure increases of siponimod up to approximately 2-fold for AUC and 1.6-fold for C_{max} is in line with the clinical DDI results. The simulated trough concentrations and exposure values in the presence of fluconazole considering genotype-based dosing were in the range of those achieved or predicted in the pivotal clinical study with SPMS patients at 2 mg across all CYP2C9 genotypes (see section 5.1 Pharmacodynamic properties - Clinical trials). Surrogate DDI assessments on strong CYP2C9 inhibitors on the basis of exposure values of siponimod in subjects with CYP2C9*3*3 genotype resulted in an approximately 4-fold exposure increase compared to CYP2C9*1*1 and therefore, the concomitant use of strong CYP2C9 inhibitors is therefore not recommended.

Co-administration of siponimod with CYP2C9 and CYP3A4 inducers

The co-administration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampicin (dual moderate CYP2C9/strong CYP3A4 inducers) decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57% and 45%, respectively in CY2C9*1*1 subjects. DDI simulations with rifampicin across all CYP2C9 genotypes (excluding CYP2C9*3*3) resulted in exposure reductions of siponimod by approximately 65%, in line with the clinical DDI results.

DDI simulations with efavirenz (a moderate CYP3A4 inducer) resulted in exposure reductions of siponimod by approximately 35% for CYP2C9*1*3 and by approximately 20% for CYP2C9*2*3 in comparison with patients with CYP2C9*1*1 genotype without concomitant medication.

Gender

Gender has no influence on siponimod pharmacokinetics.

Race/Ethnicity

The single dose PK parameters were not different between Japanese and Caucasians healthy subjects, indicating absence of ethnic sensitivity on the pharmacokinetics of siponimod.

Pharmacogenomics

The CYP2C9 genotype has a significant impact on siponimod metabolism. Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.3 to 0.4% of Caucasians and less in others) are contraindicated with Mayzent (see section 4.3 Contraindications). Use of Mayzent in these patients results in substantially elevated siponimod plasma levels. The recommended maintenance dose of Mayzent is 1 mg daily in patients with CYP2C9 *2*3 or *1*3 genotype to avoid an increased exposure to siponimod (see section 4.2 Dose and method of administration).

There are other less frequent occurring polymorphisms for CYP2C9. The pharmacokinetics of siponimod have not been evaluated in such subjects. Some polymorphisms such as *5, *6, *8 and *11 are associated with decreased or loss of enzyme function. It is estimated that CYP2C9 *5, *6, *8 and *11 alleles have a combined frequency of approximately 10% in populations with African ancestry, 2% in Latinos/Hispanics and < 0.4% in Caucasians and Asians.

After a single dose of 0.25 mg siponimod, both AUC_{inf} and AUC_{last} were approximately 2- and 4-fold higher in subjects with the CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively, while there was only a minor increase of C_{max} by 21% and 16%, respectively, compared to extensive metabolizers (CYP2C9*1*1). The mean half-life was prolonged in CYP2C9*2*3 and CYP2C9*3*3 carriers (51 and 126 h).

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1*1 and CYP2C9*1*2) SPMS patients after multiple oral administrations of siponimod. Cl/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9*2*2, CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively. As the apparent clearance estimated for subjects with the CYP2C9*1*2 genotype was comparable to that for subjects of the CYP2C9*1*1 genotype, similar siponimod exposure is expected for both genotypes. The resultant increase in siponimod AUC was 25, 61, 91, 285% in subjects with the CYP2C9*2*2, CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively, as compared to those with the CYP2C9*1*1 genotype.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vitro genotoxicity tests (bacterial mutation, micronucleus test including human cell line and chromosome aberration test using normal human lymphocytes) and in vivo micronucleus studiesusing mice and rats did not reveal genotoxic potential of siponimod.

Carcinogenicity

Consistent with an immunomodulatory effect, siponimod induced increased incidences of malignant lymphoma in mice; the human relevance is unknown.

In a carcinogenicity study in mice increased incidences of hemangiosarcomas and hemangiomas were observed at all dose levels doses in both sexes. Mechanistic studies showed activation of vascular endothelial cells, leading to induction of abnormal angiogenesis and finally hemangiosarcomas. No sustained vascular endothelial cell activation and no increased incidences of hemangiosarcomas were found in rats. Mouse, rat and human endothelial cell cultures demonstrated different responses upon siponimod treatment. Human and rat cells showed no proliferative responses as opposed to mouse cells. Therefore, the siponimod-induced hemangiosarcomas in mice are considered species-specific and there is no evidence to suggest an associated risk to humans.

In rats, siponimod-related neoplastic changes (follicular cell adenoma/carcinoma) in the thyroid gland in males only and non-neoplastic, proliferative changes in the thyroid gland (males only) and in the liver (both sexes) are considered to be due to a well-known rodent specific effect ('liver-thyroid-axis'). These changes are considered to represent adaptive effects in rodents with limited human relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate, microcrystalline cellulose, crospovidone, glycerol dibehenate and colloidal anhydrous silica.

Each 0.25 mg tablet contains 62.2 mg lactose monohydrate.

Each 1 mg tablet contains 61.4 mg lactose monohydrate.

Each 2 mg tablet contains 60.3 mg lactose monohydrate.

Tablet coating

Polyvinyl alcohol, titanium dioxide, iron oxide yellow (2 mg only), iron oxide red, black iron oxide (0.25 mg and 1 mg only), purified talc, lecithin (soya), xanthan gum.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Mayzent 0.25 mg, Mayzent 1 mg and Mayzent 2 mg:

Prior to dispensing: Store 2ºC to 8ºC (Refrigerate. Do not freeze).

After dispensing:

Mayzent 0.25 mg: Store 2ºC to 8ºC (Refrigerate. Do not freeze).

Mayzent 1 mg: Store below 30°C for up to 3 months.

Mayzent 2 mg: Store below 30°C for up to 3 months.

Store in the original package.

Information might differ in some countries.

Mayzent must be kept out of the reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

PA/Al/PVC/Al blister packs containing:

0.25 mg strength: 120 film coated tablets and 12 film coated tablets (titration pack)

1 mg strength: 28 film coated tablets

2 mg strength: 28 film coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

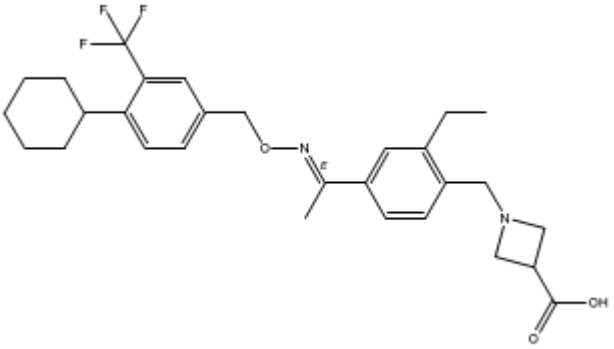
6.7 PHYSICOCHEMICAL PROPERTIES

The molecular formula for siponimod is $C_{29}H_{35}F_3N_2O_3$ and the molecular mass is 516.61.

Chemical name (IUPAC):

(2*E*)-But-2-enedioic acid—1-({4-[(1*E*)-*N*-{[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}ethanimidoyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid (1/2)

Chemical structure



CAS registry number

1230487-00-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 November 2019.

10 DATE OF REVISION

10 July 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5, 5.2	Information updated regarding CYP2C9 and CYP3A4 inhibitors & CYP2C9 and CYP3A4 inducers.
4.8	Addition of hypersensitivity as an adverse drug reaction

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