1. NAME OF THE MEDICINAL PRODUCT

Mayzent 0.25 mg film-coated tablets
Mayzent 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mayzent 0.25 mg film-coated tablets

Each film-coated tablet contains siponimod fumaric acid equivalent to 0.25 mg siponimod

Excipient with known effect
Each tablet contains 59.1 mg lactose (as monohydrate) and 0.092 mg soya lecithin.

Mayzent 2 mg film-coated tablets

Each film-coated tablet contains siponimod fumaric acid equivalent to 2 mg siponimod.

Excipient with known effect
Each tablet contains 57.3 mg lactose (as monohydrate) and 0.092 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Mayzent 0.25 mg film-coated tablets

Pale red, round, biconvex, bevelled-edged film-coated tablet of approximately 6.1 mm diameter with company logo on one side and "T" on the other side.

Mayzent 2 mg film-coated tablets

Pale yellow, round, biconvex, bevelled-edged film-coated tablet of approximately 6.1 mm diameter with company logo on one side and "II" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration

Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status (see sections 4.4, 4.5 and 5.2).
In patients with a CYP2C9*3*3 genotype, Mayzent should not be used (see sections 4.3, 4.4 and 5.2).

In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily (four tablets of 0.25 mg) (see sections 4.4 and 5.2).
The recommended maintenance dose of Mayzent in all other CYP2C9 genotype patients is 2 mg.
Mayzent is taken once daily.

Posology

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 Mayzent starting on day 6 (see Table 1). During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food.

Table 1 Dose titration regimen to reach Mayzent maintenance dosage

Titration	Titration dose	Titration regimen	Dose
Day 1	0.25 mg	1 x 0.25 mg	
Day 2	0.25 mg	1 x 0.25 mg	
Day 3	0.5 mg	2 x 0.25 mg	**TITRATION**
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]	1 x 2 mg[1]	**MAINTENANCE**

[1] In patients with CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily (4 x 0.25 mg) (see above and sections 4.4 and 5.2). Additional exposure of 0.25 mg on day 5 does not compromise patient safety.

Missed dose(s) during treatment initiation
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.

Missed dose after day 6
If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.

Re-initiation of maintenance therapy after treatment interruption
If maintenance treatment is interrupted for 4 or more consecutive daily doses, Mayzent needs to be re-initiated with a new titration pack.

Special populations
Elderly
Mayzent has not been studied in patients aged 65 years and above. Clinical studies included patients up to the age of 61 years. Mayzent should be used with caution in the elderly due to insufficient data on safety and efficacy (see section 5.2).

Renal impairment
Based on clinical pharmacology studies, no dose adjustment is needed in patients with renal impairment (see section 5.2).

Hepatic impairment
Mayzent must not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). Although no dose adjustment is needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Mayzent in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

Oral use. Mayzent is taken with or without food.

The film-coated tablets should be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance, or to peanut, soya or any of the excipients listed in section 6.1.
- 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 (see section 4.4).
- 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 (see section 4.4).
- Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser).
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Infections

Risk of infections
A core pharmacodynamic effect of Mayzent is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5.1).

The immune system effects of Mayzent may increase the risk of infections (see section 4.8).

Before initiating treatment, a recent complete blood count (CBC) (i.e., within last 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/l, if confirmed, should lead to dose reduction to 1 mg, because in clinical studies Mayzent dose was reduced in patients with absolute lymphocyte counts $<0.2 \times 10^9$/l. Confirmed absolute lymphocyte counts $<0.2 \times 10^9$/l in a patient already receiving Mayzent 1 mg should lead to interruption of Mayzent therapy until the level reaches 0.6×10^9/l when re-initiation of Mayzent can be considered.

Initiation of treatment 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, vigilance for infection should be continued throughout this period (see below section “Stopping Mayzent therapy”).

Patients should be instructed to report symptoms of infection to their physician promptly. 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. Cases of CM have been reported for another sphingosine 1-phosphate (S1P) receptor modulator. Patients with symptoms and signs consistent with CM 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 Undesirable effects). Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. If PML is suspected, Mayzent treatment should be suspended until PML has been excluded.

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

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

Live attenuated vaccines
The use of live attenuated vaccines should be avoided while patients are taking Mayzent and for 4 weeks after stopping treatment (see section 4.5).

Non-live attenuated vaccines
Non-live attenuated vaccines may be less effective if administered during Mayzent treatment. Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. 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 section "Stopping Mayzent therapy" and section 4.5). When stopping Mayzent therapy for vaccination, the possible return of disease activity should be considered (see below section "Stopping Mayzent therapy").

Concomitant treatment with anti-neoplastic, immune-modulating or immunosuppressive therapies
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).

Macular oedema

Macular oedema with or without visual symptoms was more frequently reported on Mayzent (1.8%) than on placebo (0.2%) in the phase III clinical study (A2304) (see section 4.8). The majority of cases occurred within the first 3-4 months of therapy. An ophthalmological evaluation is therefore recommended 3-4 months after treatment initiation. As cases of macular oedema have also occurred on longer-term treatment, patients should report visual disturbances at any time while on Mayzent therapy and an evaluation of the fundus, including the macula, is recommended.

Mayzent therapy should not be initiated in patients with macular oedema until resolution.

Mayzent 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 (see section 4.8). It is recommended that these patients should undergo an ophthalmological evaluation prior to initiating therapy and regularly while receiving Mayzent therapy to detect macular oedema.

Continuation of Mayzent therapy in patients with macular oedema has not been evaluated. It is recommended that Mayzent be discontinued if a patient develops macular oedema. A decision on whether or not Mayzent should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

Bradyarrhythmia

Reduction in heart rate
Initiation of Mayzent treatment results in a transient decrease in heart rate (see sections 4.8 and 5.1), and a titration scheme to reach the maintenance dose on day 6 is therefore applied at the start of treatment (see section 4.2).

After the first titration dose, the heart rate decrease starts within one 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. A few patients experienced mild to moderate symptoms including dizziness and non-cardiac chest pain, which resolved within 24 hours without intervention (see section 4.8). If necessary, the decrease in heart rate induced by Mayzent can be reversed by parenteral doses of atropine or isoprenaline.

Atrioventricular conduction
Initiation of Mayzent treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern to 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). In clinical studies, second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed in less than 1.7% of patients at the time of treatment initiation. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours and did not require discontinuation of treatment.

Treatment initiation recommendation in patients with certain pre-existing cardiac conditions
As a precautionary measure, patients with the following cardiac conditions should be observed for a period of 6 hours after the first dose of Mayzent for signs and symptoms of bradycardia (see also section 4.3):
- 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. 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.

Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, Mayzent **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 Mayzent 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.

A thorough QT study demonstrated no significant direct QT-prolonging effect and Mayzent is not associated with an arrhythmogenic potential related to QT prolongation. Initiation of 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 medicinal products. If treatment with Mayzent 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 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 (e.g., amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and class III antiarrhythmic medicinal products have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of treatment results in decreased heart rate, Mayzent should not be used concomitantly with these medicinal products during treatment initiation.

Experience 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) as these medicinal products were not studied in patients receiving Mayzent in clinical studies. Concomitant use of these substances during treatment 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 (see section 4.5). In such patients, treatment with Mayzent should be considered only if the anticipated benefits outweigh the potential risks.

If concomitant treatment with one of the above substances is considered during initiation of treatment with Mayzent, 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 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 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 (see section 4.5).

Liver function

Recent (i.e., within last 6 months) transaminase and bilirubin levels should be available before initiationof treatment with Mayzent.

In the phase III clinical study A2304, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times the upper limit of normal (ULN) was observed in 5.6% of patients treated with Mayzent 2 mg compared to 1.5% of patients who received placebo (see section 4.8). In clinical studies treatment was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic function or if the elevation exceeded a 5-fold increase. In the phase III clinical study, 1% of all discontinuations met one of these criteria.

Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked and Mayzent should be discontinued if significant liver injury is confirmed. Resumption of therapy will

be dependent on whether or not another cause of liver injury is determined and on the benefits to the patient of resuming therapy versus the risks of recurrence of liver dysfunction.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function test values when taking Mayzent, caution should be exercised in patients with a history of significant liver disease.

Cutaneous neoplasms

In study A2304, basal cell carcinoma (BCC) was the most common neoplasm and was reported with a similar incidence in the Mayzent 2 mg (1.1%) and placebo (1.3%) groups. 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 Undesirable effects). Other skin malignancies, including melanoma, have also been reported in patients treated with Mayzent and in patients on long-term therapy with another S1P modulator.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer and patients with suspicious skin lesions. Patients treated with Mayzent should be cautioned against exposure to sunlight without protection. 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 (PRES) have been reported for another sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for Mayzent in the development programme. However, should a patient on Mayzent treatment develop any unexpected neurological or psychiatric symptoms/signs (e.g. cognitive deficits, behavioural changes, cortical visual disturbances or any other neurological cortical symptoms/signs or any symptom/sign suggestive of an increase in intracranial pressure) 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 to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A peripheral lymphocyte count (CBC) is recommended prior to initiating Mayzent to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

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.

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

Blood pressure effects

Patients with hypertension uncontrolled by medication were excluded from participation in clinical studies and special care is indicated if patients with uncontrolled hypertension are treated with Mayzent.

Hypertension was more frequently reported in patients on Mayzent (12.6%) than in those given placebo (9.0%) in the phase III clinical study A2304 in patients with SPMS. Treatment with Mayzent 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 regularly monitored during treatment with Mayzent and managed appropriately.

CYP2C9 genotype

Before initiation of treatment with Mayzent, patients should be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status (see sections 4.2 and 5.2).

Women of childbearing potential

Due to risk for the foetus, Mayzent is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this 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 (see sections 4.3 and 4.6).

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 after stopping Mayzent treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon Mayzent discontinuation and appropriate treatment should be instituted as required.

After Mayzent 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.

In the vast majority (90%) of SPMS patients, lymphocyte counts return to the normal range within 10 days of stopping therapy. However, residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, 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

Since Mayzent 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 involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Excipients

The tablets contain soya lecithin. Patients who are hypersensitive to peanut or soya should not take Mayzent (see section 4.3).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Antineoplastic, immune-modulating or immunosuppressive therapies

Mayzent 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 (see section 4.4).

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with Mayzent after alemtuzmab is not recommended unless the benefits of treatment clearly outweigh the risks for the individual patient (see section 4.4).

Anti-arrhythmic medicinal products, QT-prolonging medicinal products, medicinal products that may decrease heart rate

During treatment initiation Mayzent 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 (see section 4.4). No data are available for concomitant use of these medicinal products with Mayzent. Concomitant use of these substances during treatment 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 (see section 4.4). If treatment with Mayzent 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 Mayzent is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate (see section 4.4). Beta-blocker treatment can be initiated in patients receiving stable doses of Mayzent.

The negative chronotropic effect of co-administration of Mayzent and propranolol was evaluated in a dedicated pharmacodynamic/safety study. The addition of propranolol on top of Mayzent pharmacokinetic/pharmacodynamic steady state had less pronounced negative chronotropic effects (less than additive) in comparison to addition of Mayzent on top of propranolol pharmacokinetic/pharmacodynamic 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 and for up to 4 weeks after treatment (see section 4.4).

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 resulted in influenza vaccination efficacy with responder rates approximately 15% to 30% lower than on placebo (see section 4.4).

Potential of other medicinal products to affect siponimod pharmacokinetics

Siponimod is metabolised primarily by cytochrome P450 2C9 (CYP2C9) (79.3%) and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%). CYP2C9 is a polymorphic enzyme and the drug-drug interaction (DDI) effect in the presence of CYP3A or CYP2C9 perpetrator drugs is predicted to be dependent on the CYP2C9 genotype (see section 5.2).

CYP2C9 and CYP3A4 inhibitors

Because of a significant increase in exposure to siponimod, concomitant use of Mayzent 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.

The co-administration of fluconazole (moderate CYP2C9/strong CYP3A4 inhibitor) 200 mg daily at steady state and a single dose of siponimod 4 mg in healthy volunteers with a CYP2C9*1*1 genotype led to a 2-fold increase in the area under the curve (AUC) of siponimod. According to evaluation of the drug interaction potential using physiologically based pharmacokinetic (PBPK) modelling, a maximum of a 2-fold increase in the AUC of siponimod is predicted across genotypes with any type of CYP3A4 and CYP2C9 inhibitors except for patients with a CYP2C9*2*2 genotype. In CYP2C9*2*2 patients, a 2.7-fold increase in the AUC of siponimod is expected in the presence of moderate CYP2C9/CYP3A4 inhibitors.

CYP2C9 and CYP3A4 inducers

Mayzent may be combined with most types of CYP2C9 and CYP3A4 inducers. However, because of an expected reduction in Mayzent exposure, the appropriateness and possible benefit of the treatment should be considered when Mayzent is combined:

- with strong CYP3A4/moderate CYP2C9 inducers (e.g., carbamazepine) in all patients regardless of genotype
- with moderate CYP3A4 inducers (e.g., modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype.

A significant reduction of siponimod exposure (by up to 76% and 51%, respectively) is expected under these conditions according to evaluation of the drug interaction potential using PBPK modelling. The co-administration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 inducer) decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57% and 45%, respectively, in CY2C9*1*1 subjects.

Oral contraceptives

Co-administration with Mayzent 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Mayzent is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, 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 Mayzent (see section 4.4).

Specific measures are also included in the Educational Materials. These measures must be implemented before Mayzent is prescribed to female patients and during treatment.

When stopping Mayzent therapy for planning a pregnancy, the possible return of disease activity should be considered (see section 4.4).

Pregnancy

There are no or limited amount of data available from the use of Mayzent in pregnant women. Animal studies have demonstrated Mayzent-induced embryotoxicity and foetotoxicity in rats and rabbits and teratogenicity in rats, including embryo-foetal deaths and skeletal or visceral malformations at exposure levels comparable to the human exposure at the daily dose of 2 mg (see section 5.3). In addition, clinical experience with another sphingosine-1-phosphate receptor modulator indicated a 2-fold higher risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population.

Consequently, Mayzent is contraindicated during pregnancy (see section 4.3). Mayzent should be stopped at least 10 days before a pregnancy is planned (see section 4.4). If a woman becomes pregnant while on treatment, Mayzent must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Breast-feeding

It is unknown whether Mayzent or its major metabolites are excreted in human milk. Mayzent and its metabolites are excreted in the milk of rats.

Since many drugs are transferred to 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. Mayzent should not be used during breast-feeding.

Fertility

The effect of Mayzent on human fertility has not been evaluated. Mayzent had no effect on male reproductive organs in rats and monkeys or on fertility parameters in rats.

4.7 Effects on ability to drive and use machines

Mayzent has no or negligible influence on the ability to drive and use machines. However, dizziness may occasionally occur when initiating therapy with Mayzent. Therefore, patients should not drive or use machines during the first day of treatment initiation with Mayzent (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions are headache (15%) and hypertension (12.6%).

Tabulated list of adverse reactions

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: 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 Tabulated list of adverse reactions

Infections and infestations	
Common	Herpes zoster
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Common	Melanocytic naevus, basal cell carcinoma
Uncommon	Squamous cell carcinoma
Blood and lymphatic system disorders	
Common	Lymphopenia
Nervous system disorders	
Very common	Headache
Common	Dizziness Seizure Tremor
Eye disorders	
Common	Macular oedema
Cardiac disorders	
Common	Bradycardia Atrioventricular block (first and second degree)
Vascular disorders	
Very common	Hypertension
Gastrointestinal disorders	
Common	Nausea Diarrhoea
Musculoskeletal and connective tissue disorders	
Common	Pain in extremity
General disorders and administration site conditions	
Common	Oedema peripheral Asthenia
Investigations	
Very common	Liver function test increased
Common	Pulmonary function test decreased

Description of selected adverse reactions

Infections

In the phase III clinical study A2304 in patients with SPMS, the overall rate of infections was comparable between the patients on siponimod and those on placebo (49.0% versus 49.1%, respectively). However, an increase in the rate of herpes zoster infections was reported on siponimod (2.5%) compared to placebo (0.7%). Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by varicella zoster virus, have been reported with Mayzent. Cases of progressive multifocal leukoencephalopathy and cryptococcal meningitis (CM) have been reported with Mayzent (see section 4.4).

Macular oedema

Macular oedema was more frequently reported in patients receiving siponimod (1.8%) than in those given 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 months (see section 4.4). Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmological examination. The macular oedema generally improved or resolved spontaneously after discontinuation of treatment. 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 atrioventricular conduction delays (see section 4.4). Bradycardia was reported in 6.2% of patients

treated with Mayzent compared to 3.1% on placebo and AV block in 1.7% of patients treated with Mayzent compared to 0.7% on placebo (see section 4.4).

The maximum decline in heart rate is seen in the first 6 hours post-dose.

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

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 siponimod t can be reversed by atropine or isoprenaline.

Liver function tests
Increased hepatic enzymes (mostly ALT elevation) have been reported in MS patients treated with siponimod. In the phase III study A2304 in patients with SPMS, liver function test increases were more frequently observed in patients on siponimod (11.3%) than in those on placebo (3.1%), mainly due to liver transaminase (ALT/AST) and 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).

Blood pressure
Hypertension was more frequently reported in patients on siponimod (12.6%) than in those given placebo (9.0%) in the phase III clinical study 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.

Seizures
Seizures were reported in 1.7% of patients treated with Mayzent compared to 0.4% on placebo in the phase III clinical study A2304 in patients with SPMS.

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 Mayzent treatment. At months 3 and 6 of treatment in the phase III clinical study A2304 in patients with SPMS, mean changes from baseline in FEV_1 in the Mayzent group were -0.1 L at each time point, with no change in the placebo group. These observations were slightly higher (approximately 0.15 L mean change from baseline in FEV_1) in patients with respiratory disorders such as chronic obstructive pulmonary disease (COPD) or asthma treated with Mayzent. 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 dyspnoea (see section 5.1).

4.9 Overdose

In healthy subjects, the single maximum tolerated dose was determined to be 25 mg based upon the occurrence of symptomatic bradycardia after single doses of 75 mg. A few subjects received unintended doses of up to 200 mg daily for 3 to 4 days and experienced asymptomatic mild to moderate transient elevations of liver function tests.

One patient (with a history of depression) who took 84 mg siponimod experienced a slight elevation in liver transaminases.

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 and 4.4).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA42

Mechanism of action

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds selectively to 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.

Pharmacodynamic effects

Reduction of the peripheral blood lymphocytes
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 (0.271-1.08) cells/nL in a typical CYP2C9*1*1 or *1*2 non-Japanese SPMS patient, corresponding to 20-30% of baseline. Low lymphocyte counts are maintained with daily dosing.

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

Heart rate and rhythm
Mayzent causes a transient reduction in heart rate and atrioventricular conduction on treatment initiation (see sections 4.4 and 4.8), which is mechanistically related to the activation of G-protein-coupled inwardly rectifying potassium (GIRK) channels via S1P1 receptor stimulation leading to cellular hyperpolarisation and reduced excitability. Due to its functional antagonism at S1P1 receptors, initial titration of Mayzent successively desensitises GIRK channels until the maintenance dose is reached.

Potential to prolong the QT interval
The effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of Mayzent on cardiac repolarisation were investigated in a thorough QT study. The results did not suggest an arrhythmogenic potential related to QT prolongation with Mayzent. Mayzent 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 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 (FEV_1) and forced expiratory flow (FEF) during expiration of 25 to 75% of the forced vital capacity ($FEF_{25-75\%}$). A slight

trend of reduced FEV_1 was detected at non-therapeutic single doses (>10 mg). Multiple doses of Mayzent were associated with mild to moderate changes in FEV_1 and $FEF_{25-75\%}$ 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 efficacy and safety

The efficacy of Mayzent has been investigated in a phase III study evaluating once-daily doses of 2 mg in patients with SPMS.

Study A2304 (EXPAND)
Study A2304 was a randomised, double-blind, placebo-controlled, event and follow-up duration driven, phase III 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 the 3 months prior to study enrolment and with a median Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at study entry. The median EDSS was 6.0 at baseline. Patients above 61 years of age were not included. With regard to disease activity, features characteristic of inflammatory activity in SPMS can be relapse- or imaging-related (i.e. Gd-enhancing T1 lesions or active [new or enlarging] T2 lesions).

Patients were randomised 2:1 to receive either once-daily Mayzent 2 mg or placebo. Clinical 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 (T25W) and change from baseline in T2 lesion volume. Additional secondary endpoints included time to 6-month CDP, percent brain volume change and measures of inflammatory disease activity (annualised relapse rate, MRI lesions). Change in cognitive processing speed on Symbol Digit Modality Test score was an exploratory endpoint.

Study duration was variable for individual patients (median study duration was 21 months, range: 1 day to 37 months).

The study involved randomisation of 1,651 patients to either Mayzent 2 mg (N=1,105) or placebo (N=546); 82% of patients treated with Mayzent and 78% of placebo-treated patients completed the study. Median age was 49 years, median disease duration was 16 years and median EDSS score was 6.0 at baseline. 64% of patients had no relapses in the 2 years prior to study entry and 76% had no gadolinium (Gd)-enhancing lesions on their baseline MRI scan. 78% of patients had been previously treated with a therapy for their MS.

Time to onset of 3-month and 6-month CDP was significantly delayed for Mayzent, with reduction in risk of 3-month CDP by 21% compared to placebo (hazard ratio [HR] 0.79, p=0.0134) and reduction in risk of 6-month CDP by 26% compared to placebo (HR 0.74, p=0.0058).

Figure 1 Patients with 3- and 6-month CDP based on EDSS-Kaplan-Meier curves (full analysis set, study A2304)

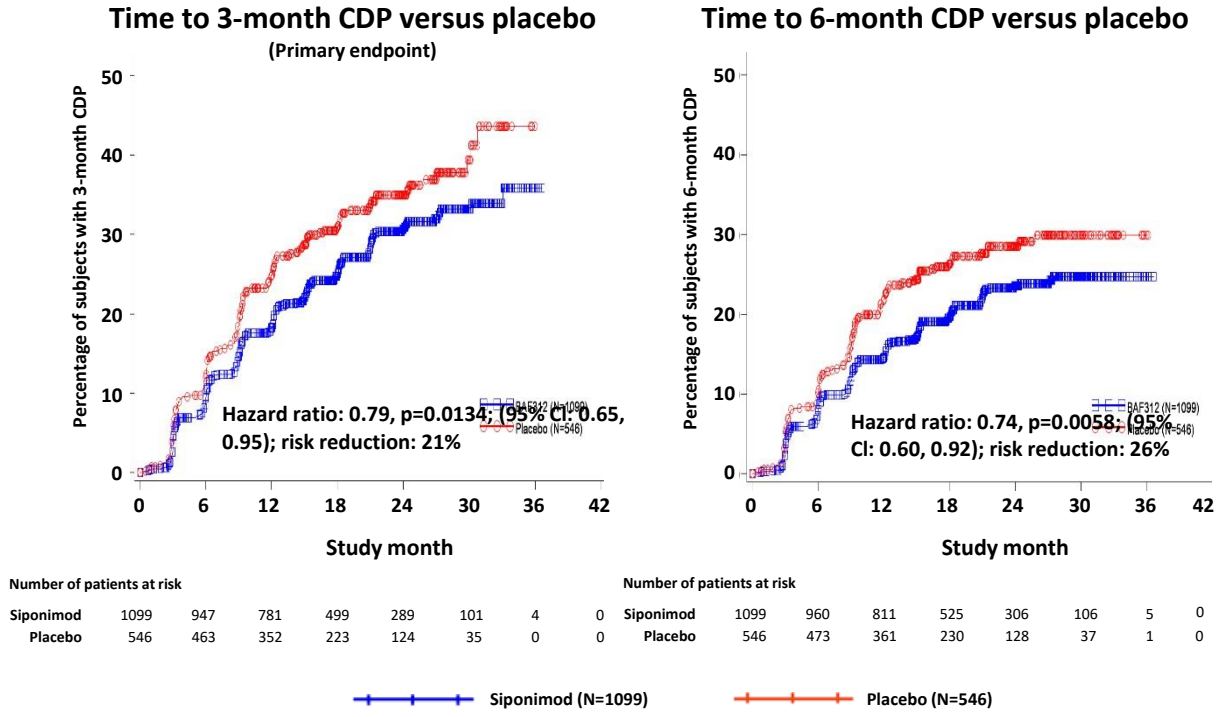


Table 3 Clinical and MRI results of study A2304

Endpoints	**A2304 (EXPAND)**	
	Mayzent 2 mg (n=1,099)	**Placebo (n=546)**
Clinical endpoints		
Primary efficacy endpoint: Proportion of patients with 3-month confirmed disability progression (primary endpoint)	26.3%	31.7%
Risk reduction[1]	21% (p=0.0134)	
Proportion of patients with 3-month confirmed 20% increase in timed 25-foot walk test	39.7%	41.4%
Risk reduction[1]	6% (p=0.4398)	
Proportion of patients with 6-month confirmed disability progression	19.9%	25.5%
Risk reduction[1]	26% *[(p=0.0058)]*[6]	
Annualised relapse rate (ARR)	0.071	0.152
Rate reduction[2]	55% *[(p<0.0001)]*[6]	
MRI endpoints		
Change from baseline in T2 lesion volume (mm^3)[3]	+184 mm^3	+879 mm^3
Difference in T2 lesion volume change	-695 mm^3 (p<0.0001)[7]	
Percentage brain volume change relative to baseline (95% CI)[3]	-0.497%	-0.649%
Difference in percentage brain volume change	0.152% *[(p=0.0002)]*[6]	
Average cumulative number of Gd-enhancing T1 weighted lesions (95% CI)[4]	0.081	0.596
Rate reduction	86% *[(p<0.0001)]*[6]	
Proportion of patients with 4-point worsening in Symbol Digit Modality Test[5]	16.0%	20.9%
Risk reduction[1]	25% *[(p=0.0163)]*[6]	

1 From Cox modelling for time to progression
2 From a model for recurrent events
3 Average over month 12 and month 24
4 Up to month 24
5 Confirmed at 6 months
6 *[Nominal p-value for endpoints not included in the hierarchical testing and not adjusted for multiplicity]*
7 Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint

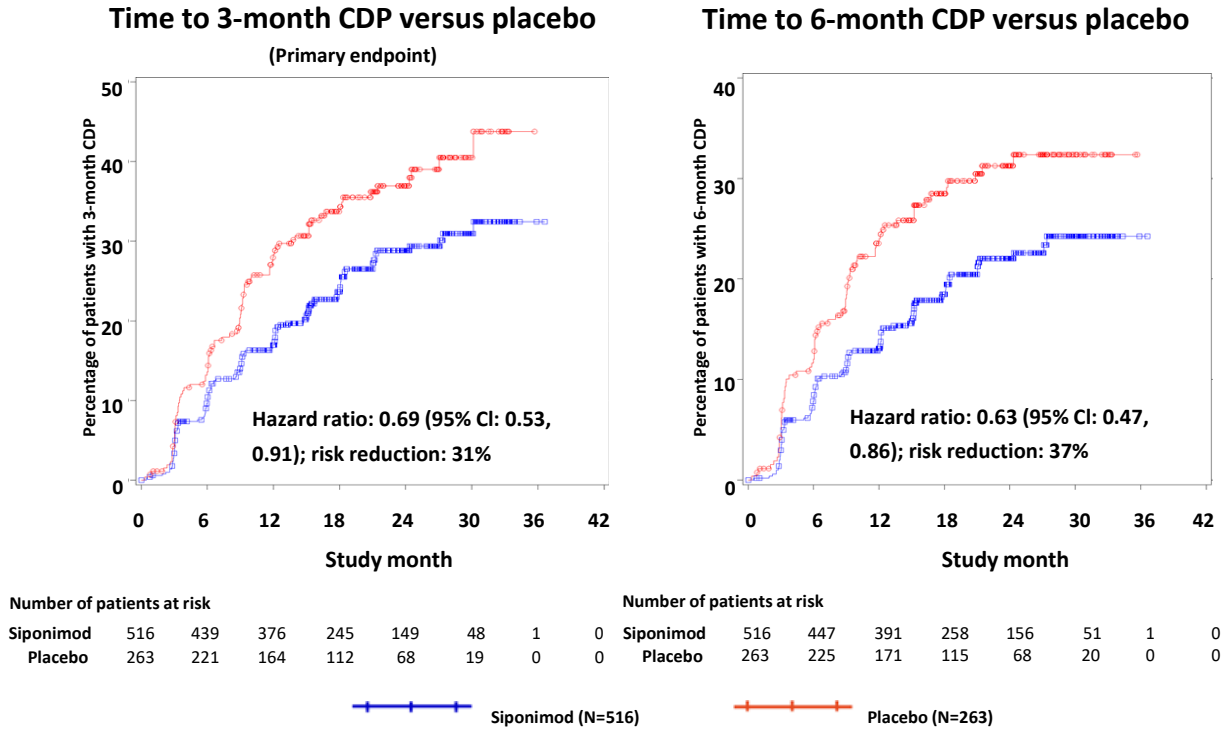
Results from the study showed a variable but consistent risk reduction in the time to 3- and 6-month CDP with Mayzent compared to placebo in subgroups defined based on gender, age, pre-study relapse activity, baseline MRI disease activity, disease duration and disability levels at baseline.

In the subgroup of patients (n=779) with active disease (defined as patients with relapse in the 2 years prior to the study and/or presence of Gd-enhancing T1 lesions at baseline) the baseline characteristics were similar to the overall population. Median age was 47 years, median disease duration was 15 years and median EDSS score at baseline was 6.0.

Time to onset of 3-month and 6-month CDP was significantly delayed in Mayzent-treated patients with active disease, by 31% compared to placebo (hazard ratio [HR] 0.69; 95% CI: 0.53, 0.91) and by 37% compared to placebo (HR 0.63; 95% CI: 0.47, 0.86), respectively. The ARR (confirmed relapses) was reduced by 46% (ARR ratio 0.54; 95% CI: 0.39, 0.77) compared to placebo. The relative rate reduction of cumulative number of Gd-enhancing T1 weighted lesions over 24 months was 85% (rate ratio 0.155; 95% CI: 0.104, 0.231) compared to placebo. The differences in T2 lesion volume change and in

percentage of brain volume change (average over months 12 and 24) compared to placebo were -1163 mm^3 (95% CI: -1484, -843 mm^3) and 0.141% (95% CI: 0.020, 0.261%), respectively.

Figure 2 Patients with 3- and 6-month CDP based on EDSS-Kaplan-Meier curves – Subgroup with active SPMS (full analysis set, study A2304)



In the subgroup of patients (n=827) without signs and symptoms of disease activity (defined as patients without relapse in the 2 years prior to the study and without presence of Gd-enhancing T1 lesions at baseline), effects on 3-month and 6-month CDP were small (risk reductions were 7% and 13%, respectively).

5.2 Pharmacokinetic properties

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after multiple oral administration of siponimod is 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 faeces 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.

Despite a delay in T_{max} to 8 hours after a single dose, 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).

Distribution

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

Biotransformation

Siponimod is extensively metabolised, mainly by cytochrome P450 2C9 (CYP2C9) (79.3%), and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%).

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.

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.

CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. PBPK modelling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated (see section 4.5).

Elimination

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

Siponimod is eliminated from the systemic circulation mainly due to metabolism and subsequent biliary/faecal excretion. Unchanged siponimod was not detected in urine.

Linearity

Siponimod concentration increases in an apparent dose proportional manner after multiple once-daily doses of siponimod 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 after the initial dose. An up-titration regimen is used to reach the clinically therapeutic dose of 2 mg siponimod after 6 days and 4 additional days of dosing are required to reach the steady-state plasma concentrations.

Characteristics in specific groups or special populations

CYP2C9 genotype
The CYP2C9 genotype influences siponimod CL/F. Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.3 to 0.4% of the population) should not be treated with Mayzent. Use of Mayzent in these patients results in substantially elevated Mayzent plasma levels. The recommended maintenance dose is 1 mg daily in patients with a CYP2C9*2*3 genotype (1.4-1.7% of the population) and in patients with a *1*3 genotype (9-12% of the population) to avoid increased exposure to Mayzent (see sections 4.2 and 5.2).

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.

Two population pharmacokinetic analyses indicated that CYP2C9*1*1 and *1*2 subjects behave as extensive metabolisers, *2*2 and *1*3 subjects as intermediate metabolisers and *2*3 and *3*3 subjects

as poor metabolisers. Compared to CYP2C9*1*1 subjects, individuals with the CYP2C9*2*2, *1*3, *2*3 and *3*3 genotypes have 20%, 35-38%, 45-48% and 74% smaller CL/F values, respectively. Siponimod exposure is therefore approximately 25%, 61%, 91% and 284% higher in CYP2C9*2*2, *1*3, *2*3 and *3*3 subjects, respectively, as compared to *1*1 subjects (see Table 4) (see sections 4.2 and 4.4).

Table 4 CYP2C9 genotype effect on siponimod CL/F and systemic exposure

CYP2C9 genotype	Frequency in Caucasians	Estimated CL/F (L/h)	% of CYP2C9*1*1 CL/F	% exposure increase versus CYP2C9*1*1
Extensive metabolisers				
CYP2C9*1*1	62-65	3.1-3.3	100	-
CYP2C9*1*2	20-24	3.1-3.3	99-100	-
Intermediate metabolisers				
CYP2C9*2*2	1-2	2.5-2.6	80	25
CYP2C9*1*3	9-12	1.9-2.1	62-65	61
Poor metabolisers				
CYP2C9*2*3	1.4-1.7	1.6-1.8	52-55	91
CYP2C9*3*3	0.3-0.4	0.9	26	284

Elderly
Results from population pharmacokinetics suggest that dose adjustment is not necessary in elderly patients (age 65 years and above). No patients over 61 years of age were enrolled in clinical studies. Mayzent should be used with caution in the elderly (see section 4.2).

Gender
Results from population pharmacokinetics suggest that gender-based dose adjustment is not necessary.

Race/Ethnicity
The single-dose pharmacokinetic parameters were not different between Japanese and Caucasian healthy subjects, indicating absence of ethnic sensitivity on the pharmacokinetics of siponimod.

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 subjects 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 haemodialysis on the pharmacokinetics of siponimod have not been studied. Due to the high plasma protein binding (>99.9%) of siponimod, haemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations.

Hepatic impairment
Siponimod must not be used in patients with severe hepatic impairment (see section 4.3). No dose adjustments for siponimod are needed in patients with mild or moderate 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.

5.3 Preclinical safety data

In repeat-dose toxicity studies in mice, rats and monkeys, siponimod markedly affected the lymphoid system (lymphopenia, lymphoid atrophy and reduced antibody response), which is consistent with its primary pharmacological activity at S1P1 receptors (see section 5.1).

Dose-limiting toxicities in animal species were nephrotoxicity in mice, body weight development in rats and adverse CNS and gastrointestinal effects in monkeys. The main target organs of toxicity in rodents included the lung, liver, thyroid, kidney and uterus/vagina. In monkeys, effects on muscle and skin were additionally observed. These toxicities developed at more than 30-fold higher systemic siponimod levels than the AUC-based human exposure at the maintenance dose of 2 mg/day.

Siponimod did not exert any phototoxic or dependence potential and was not genotoxic *in vitro* and *in vivo*.

Carcinogenicity

In carcinogenicity investigations, siponimod induced lymphoma, haemangioma and haemangiosarcoma in mice, whereas follicular adenoma and carcinoma of the thyroid gland were identified in male rats. These tumour findings were either regarded as mouse-specific or attributable to metabolic liver adaptations in the particularly sensitive rat species and are of questionable human relevance.

Fertility and reproductive toxicity

Siponimod did not affect male and female fertility in rats up to the highest dose tested, representing an approximate 19-fold safety margin based on human systemic exposure (AUC) at a daily dose of 2 mg.

The receptor affected by siponimod (sphinosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

In embryofoetal development studies conducted in rats and rabbits, siponimod induced embryotoxic effects in the absence of maternal toxicity. In both species, prenatal mortality was increased. While in rats a higher number of foetuses with external, skeletal and visceral malformations (e.g., cleft palate and misshapen clavicles, cardiomegaly and oedema) were noted, in rabbit foetuses skeletal and visceral variations were predominantly observed.

In the prenatal and postnatal development study performed in rats, there was in increased number of dead (stillborn or found dead before postnatal day 4) and malformed pups (male pups with urogenital malformations and/or decreased anogenital distance; pups of both sexes with oedema, swollen soft cranium, or flexed hindlimbs).

The exposure levels (AUC) at the respective NOAELs for embryofoetal (rats and rabbits) and pre/postnatal (rats) development were below the human systemic exposure (AUC) at a daily dose of 2 mg and consequently no safety margin exists.

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 2 mg tablet contains 60.3 mg lactose monohydrate.

Tablet coating

0.25 mg tablet: Polyvinyl alcohol, titanium dioxide (E171), black iron oxide (E172), red iron oxide (E172), talc, lecithin (soya), xanthan gum
2 mg tablet: Polyvinyl alcohol, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide

(172), talc, lecithin (soya), xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator between 2°C to 8°C.

Store in the original package.

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

6.5 Nature and contents of container

Mayzent 0.25 mg film-coated tablets

Titration packs of 12 film-coated tablets in PA/alu/PVC/alu blister.
Packs of 120 film-coated tablets in PA/alu/PVC/alu blisters.

Mayzent 2 mg film-coated tablets

Packs of 28 film-coated tablets in PA/alu/PVC/alu blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements

Country Specific Package Leaflet