ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 0.25 mg film-coated tablets
Mayzent 1 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.

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

Mayzent 1 mg film-coated tablets

Each film-coated tablet contains siponimod fumaric acid equivalent to 1 mg siponimod.

Excipients with known effect
Each tablet contains 58.3 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.

Excipients 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 1 mg film-coated tablets

Violet white, round, biconvex, bevelled-edged film-coated tablet of approximately 6.1 mm diameter with company logo on one side and “L” 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

Treatment with siponimod should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

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, siponimod should not be used (see sections 4.3, 4.4 and 5.2).

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 siponimod 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 maintenance dose

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 (1 x 1 mg or 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.

Treatment maintenance
In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg (see sections 4.4 and 5.2).

The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg.

Mayzent is taken once daily.

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, siponimod needs to be re-initiated with a new titration pack.

Special populations
Elderly
Siponimod has not been studied in patients aged 65 years and above. Clinical studies included patients up to the age of 61 years. Siponimod should be used with caution in the elderly due to insufficient data on safety and efficacy (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
Siponimod 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 siponimod in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

Oral use. Siponimod 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 siponimod 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 siponimod 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 3 to 4 months after treatment initiation and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte counts $<0.2 \times 10^9$/l, if confirmed, should lead to dose reduction to 1 mg, because in clinical studies siponimod 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 siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches 0.6×10^9/l when re-initiation of siponimod 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 siponimod 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 siponimod should be considered if a patient develops a serious infection.

Cases of cryptococcal meningitis (CM) have been reported for siponimod. Patients with symptoms and signs consistent with CM should undergo prompt diagnostic evaluation. Siponimod treatment should be suspended until CM has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive multifocal leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have been reported with siponimod (see section 4.8). Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. If PML is suspected, siponimod treatment should be suspended until PML has been excluded. If PML is confirmed, treatment with siponimod should be discontinued.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with sphingosine 1-phosphate (S1P) receptor modulators, including siponimod, 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 usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Herpes viral infection
Cases of herpes viral infection (including cases of meningitis or meningoencephalitis caused by varicella zoster viruses [VZV]) have occurred with siponimod at any time during treatment. If herpes meningitis or meningoencephalitis occur, siponimod should be discontinued and appropriate treatment for the respective infection should be administered. 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 siponimod (see below section “Vaccination”).

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

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

Other types of vaccines may be less effective if administered during siponimod treatment (see section 4.5). Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. If stopping siponimod therapy for vaccination, the possible return of disease activity should be considered (see below section "Stopping siponimod 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 siponimod (1.8%) than on placebo (0.2%) in the phase III clinical study (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 siponimod therapy and an evaluation of the fundus, including the macula, is recommended.

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

Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema (see section 4.8). It is recommended that these patients should undergo an ophthalmological evaluation prior to initiating therapy and regularly while receiving siponimod therapy to detect macular oedema.

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

Bradyarrhythmia

Initiation of siponimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see sections 4.8 and 5.1). 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. 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.

Most of the bradyarrhythmic events or atrioventricular conduction delays were asymptomatic, transient and resolved within 24 hours and did not require discontinuation of treatment. Should post-dose symptoms occur (dizziness, non-cardiac chest pain and headache), appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. If necessary, the decrease in heart rate induced by siponimod can be reversed by parenteral doses of atropine or isoprenaline.

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 siponimod 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,
- 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, siponimod **should not be used** in patients with:
- history of symptomatic bradycardia or recurrent syncope,
- uncontrolled hypertension, or
- severe untreated sleep apnoea.

In such patients, treatment with siponimod should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

A thorough QT study demonstrated no significant direct QT-prolonging effect and siponimod 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. Siponimod was not studied in patients with significant QT prolongation (QTc >500 msec) or who were treated with QT-prolonging medicinal products. If treatment with siponimod is considered in patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy during treatment initiation.

Siponimod 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, siponimod 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 siponimod 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 siponimod should generally not be initiated in patients who are concurrently treated with these substances (see section 4.5). In such patients, treatment with siponimod 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 siponimod, advice from a cardiologist should be sought regarding the switch to a non-heart-rate-lowering medicinal product or appropriate monitoring for treatment initiation.

Bradyarrhythmic effects are more pronounced when siponimod is added to beta-blocker therapy. For patients receiving a stable dose of beta blocker, the resting heart rate should be considered before introducing treatment. If the resting heart rate is >50 bpm under chronic beta-blocker treatment, siponimod 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 siponimod can then be initiated and treatment with beta blocker can be re-initiated after siponimod 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 initiation of treatment with siponimod.

In the phase III clinical study, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times the upper limit of normal (ULN) was observed in 5.6% of patients treated with siponimod 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 siponimod 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 siponimod, caution should be exercised in patients with a history of significant liver disease.

Cutaneous neoplasms

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including squamous cell carcinoma (SCC) and malignant melanoma, have been reported in patients receiving siponimod, especially in patients with longer treatment duration (see section 4.8).

Skin examination is recommended for all patients at treatment initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy.

Unexpected neurological or psychiatric symptoms/signs

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 siponimod in the development programme. However, should a patient on siponimod 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 siponimod 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 siponimod after alemtuzumab is not recommended.

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

Blood pressure effects

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

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.

Blood pressure should be regularly monitored during treatment with siponimod.

CYP2C9 genotype

Before initiation of treatment with siponimod, patients should be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status (see section 4.2). Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.3 to 0.4% of the population) should not be treated with siponimod. Use of siponimod in these patients results in substantially elevated siponimod 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 siponimod (see sections 4.2 and 5.2).

Women of childbearing potential

Due to risk for the foetus, siponimod 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 siponimod therapy

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping siponimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon siponimod discontinuation and appropriate treatment should be instituted as required.

After siponimod therapy has been stopped, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

After stopping siponimod therapy in the setting of PML, it is recommended to monitor the patient for development of immune reconstitution inflammatory syndrome (PML-IRIS) (see above section "Progressive multifocal leukoencephalopathy").

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 siponimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with siponimod. 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 siponimod (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

Siponimod has not been studied in combination with antineoplastic, immune-modulating or immunosuppressive therapies. Caution should be exercised during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks after administration of any of these medicinal products is stopped (see section 4.4).

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with siponimod 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 siponimod should not be concomitantly used in patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate (see section 4.4). No data are available for concomitant use of these medicinal products with siponimod. 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 siponimod should generally not be initiated in patients who are concurrently treated with these substances (see section 4.4). If treatment with siponimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate-lowering medicinal products or appropriate monitoring for treatment initiation.

Beta blockers

Caution should be exercised when siponimod is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate (see section 4.4). Beta-blocker treatment can be initiated in patients receiving stable doses of siponimod.

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

Vaccination

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during siponimod treatment and for 4 weeks after treatment (see section 4.4).

During and for up to 4 weeks after treatment with siponimod vaccinations may be less effective. The efficacy of vaccination is not considered to be compromised if siponimod treatment is paused 1 week prior to vaccination until 4 weeks after vaccination. In a dedicated phase I healthy volunteer study, concomitant siponimod treatment with influenza vaccines or shorter treatment pause (from 10 days prior to 14 days after vaccination) showed inferior responder rates (approximately 15% to 30% lower) compared to placebo, while the efficacy of a PPV 23 vaccination was not compromised by concomitant siponimod treatment (see section 4.4).

Potential of other medicinal products to affect siponimod pharmacokinetics

Cytochrome P450 (CYP2C9) is the major metabolising enzyme for siponimod, accounting for 79.5% of metabolism in extensive metabolisers with the CYP2C9*1*1 genotype. Residual elimination of siponimod is ascribed to various other cytochromes, each of which is responsible for a minor fraction of elimination.

CYP2C9 inhibitors
Concomitant use of siponimod and medicinal products that cause moderate or strong CYP2C9 inhibition is not recommended because a clinically relevant increase of siponimod exposure by 2- or 4-fold is anticipated, respectively.

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 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 2.2-fold increase in the AUC is predicted with any type of moderate CYP2C9 inhibitor depending on the CYP2C9 genotype.

CYP2C9 and CYP3A4 inducers

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

- with dual strong CYP3A4/moderate CYP2C9 inducers (e.g. rifampicin, carbamazepine) in all patients, regardless of genotype. Co-administration of 2 mg siponimod and 600 mg rifampicin decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57% and 45%, respectively, in CYP2C9*1*1 subjects.
- with moderate CYP3A4 inducers (e.g. efavirenz, modafinil) for patients with a CYP2C9*1*3 or *2*3 genotype. The most pronounced reduction of siponimod exposure by 35% ($AUC_{tau,ss}$) and 39% ($C_{max,ss}$) is predicted after co-administration of 1 mg siponimod daily and 600 mg efavirenz daily in patients with CYP2C9*1*3 genotype compared to those with CYP2C9*1*1 genotype receiving their recommended dose of 2 mg siponimod without concomitant medication. No clinical data for siponimod combined with moderate CYP3A4 inducers are available.

Oral contraceptives

Co-administration with siponimod did not reveal clinically relevant effects on the pharmacokinetics and pharmacodynamics of the combined ethinylestradiol and levonorgestrel oral contraceptive. Therefore the efficacy of the investigated oral contraceptive was maintained under siponimod treatment.

No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of siponimod on the efficacy of oral contraceptives is not expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Siponimod 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 siponimod (see section 4.4).

Specific measures are also included in the Physician Education Pack. These measures must be implemented before siponimod is prescribed to female patients and during treatment.

When stopping siponimod 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 siponimod in pregnant women. Animal studies have demonstrated siponimod-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, siponimod is contraindicated during pregnancy (see section 4.3). Siponimod should be stopped at least 10 days before a pregnancy is planned (see section 4.4). If a woman becomes pregnant while on treatment, siponimod 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 siponimod or its major metabolites are excreted in human milk. Siponimod and its metabolites are excreted in the milk of rats. Siponimod should not be used during breast-feeding.

Fertility

The effect of siponimod on human fertility has not been evaluated. Siponimod 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

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile of siponimod was based on data from the core clinical study. The most common adverse reactions identified in the core part of study A2304 were headache (15%) and hypertension (12.6%). The safety-related information from the extension part of the long-term study A2304 was consistent with that observed in the core part.

Tabulated list of adverse reactions

Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse 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); not known (cannot be estimated from the available data).

Table 2 Tabulated list of adverse reactions

Infections and infestations	
Common	Herpes zoster
Rare	Progressive multifocal leukoencephalopathy
Not known	Meningitis cryptococcal
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Common	Melanocytic naevus Basal cell carcinoma
Uncommon	Squamous cell carcinoma Malignant melanoma
Blood and lymphatic system disorders	
Common	Lymphopenia
Immune system disorders	
Rare	Immune reconstitution inflammatory syndrome (IRIS)
Not known	Hypersensitivity reactions, including rash, urticaria and angioedema

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 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 meningitis or meningoencephalitis caused by varicella zoster viruses have occurred with siponimod at any time during treatment. Cases of cryptococcal meningitis (CM) have also been reported for siponimod (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 siponimod compared to 3.1% on placebo and AV block in 1.7% of patients treated with siponimod 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 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 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 siponimod compared to 0.4% on placebo in the phase III clinical study 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 siponimod treatment. At months 3 and 6 of treatment in the phase III clinical study in patients with SPMS, mean changes from baseline in FEV_1 in the siponimod 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 siponimod. 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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 siponimod or occurs during the dose titration phase of siponimod 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 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: 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 to two out of five G-protein-coupled receptors (GPCRs) for S1P, namely S1P1 and S1P5. By acting as a functional antagonist on S1P1 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
Siponimod 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 siponimod treatment residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose.

Heart rate and rhythm
Siponimod 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 siponimod 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 siponimod on cardiac repolarisation 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 ($\Delta\Delta$QTcF) 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 $\Delta\Delta$QTcF 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
Siponimod 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 siponimod 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.

Clinical efficacy and safety

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

Study A2304 (EXPAND) in SPMS
The core part of 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 an 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 siponimod 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 siponimod 2 mg (N=1 105) or placebo (N=546); 82% of patients treated with siponimod 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 siponimod, 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)

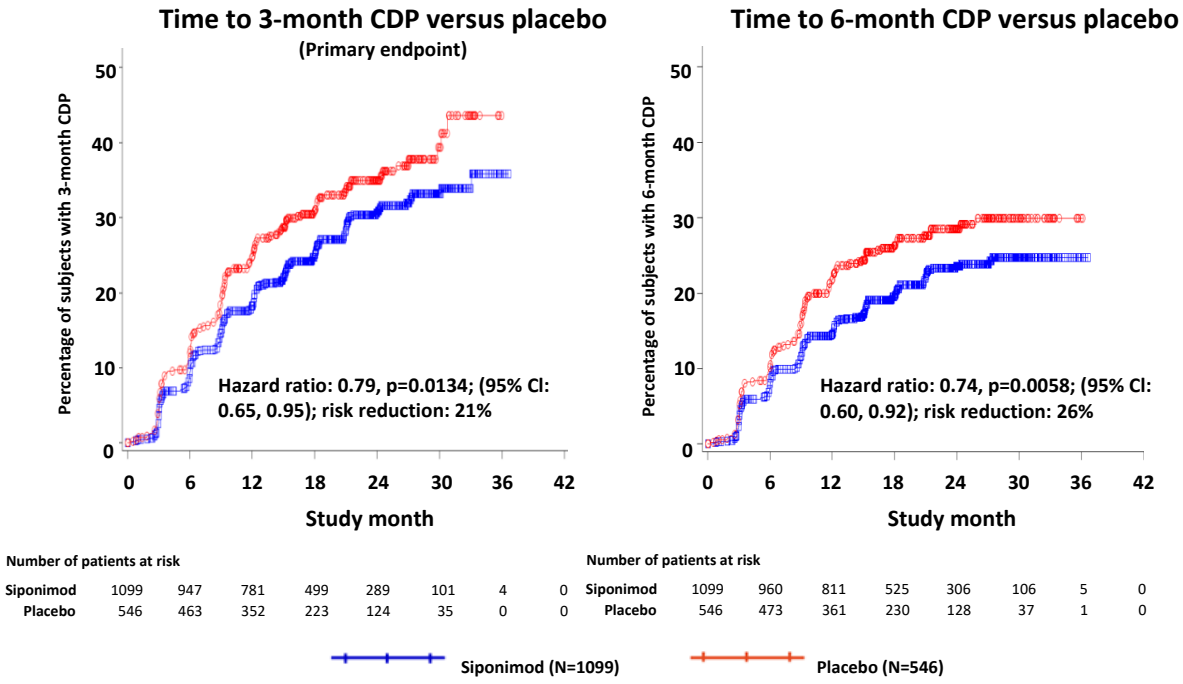


Table 3 Clinical and MRI results of study A2304

Endpoints	A2304 (EXPAND)	
	Siponimod 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]	

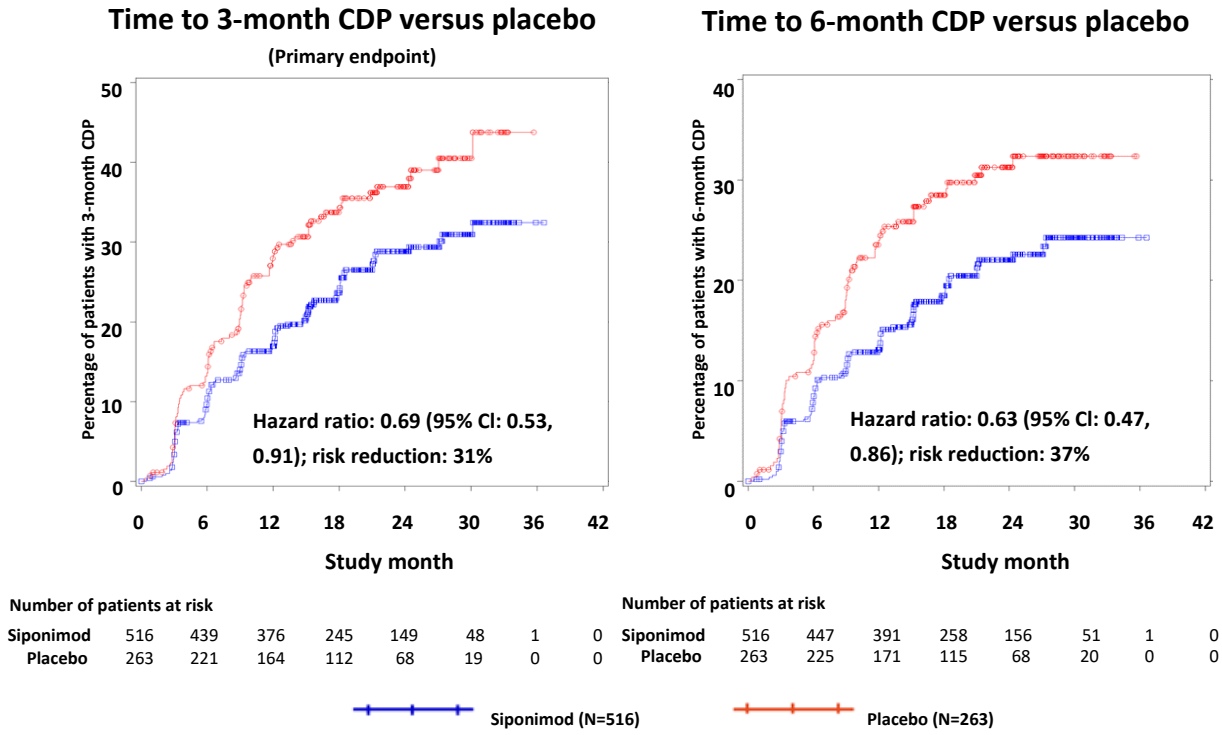
[1] From Cox modelling for time to progression
[2] From a model for recurrent events
[3] Average over month 12 and month 24
[4] Up to month 24
[5] Confirmed at 6 months
[6] *[Nominal p-value for endpoints not included in the hierarchical testing and not adjusted for multiplicity]*
[7] Non-confirmatory 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 siponimod 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 siponimod-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 -1 163 mm^3 (95% CI: -1 484, -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).

A post-hoc analysis of study A2304 (EXPAND) showed that siponimod delayed progression to EDSS ≥7.0 (sustained until end of study, i.e. time to wheelchair), resulting in a risk reduction of 38% (HR from Cox model 0.62; 95% CI: 0.41, 0.92). The Kaplan-Meier estimate of percentage of patients progressed to EDSS ≥7.0 at month 24 was 6.97% in the siponimod group and 8.72% in the placebo group. In the subgroup of patients with active SPMS, the risk reduction was 51% (HR 0.49; 95% CI: 0.27, 0.90) and the Kaplan-Meier estimates at month 24 were 6.51% in the siponimod group and 8.69% in the placebo group. As these results were exploratory in nature, they should be interpreted with caution.

The core part (CP) of study A2304 was followed by a single-arm, open-label extension part (EP). The EP objective was exploratory in nature and in place to evaluate long-term efficacy and safety of siponimod for up to 7 additional years' treatment. Of the total number of patients randomised, 68% (n=1 120) entered and 29% (n=485) completed the EP of study A2304. The Kaplan-Meier estimate of percentage of patients with 6-month CDP at month 108 was 64.7% in the continuous siponimod group and 68.4% in the group of patients who switched from placebo to siponimod after CP. In patients with active SPMS, the Kaplan-Meier estimate of percentage of patients with 6-month CDP at month 108 was 62.9% in the continuous siponimod group and 68.1% in the group of patients who switched from placebo to siponimod after the CP.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with siponimod in one or more subsets of the paediatric population in the treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

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 siponimod 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 polymorphic CYP2C9 (79.5% for 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.

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.

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.

Drug-drug interaction (DDI)

The impact of moderate CYP2C9 inhibitors on siponimod exposure was observed and predicted to be up to 2-fold for AUC and 1.6-fold for C_{max} across all CYP2C9 genotypes at the maintenance dose. DDI predictions for strong CYP2C9 inhibitors resulted in an approximately 4-fold exposure increase compared to CYP2C9*1*1. The concomitant use of moderate or strong CYP2C9 inhibitors is therefore not recommended (see section 4.5).

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 that was not clinically relevant.

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. 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).

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.

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. Siponimod 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

Mayzent 0.25 mg film-coated tablets

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Crospovidone
Glycerol dibehenate
Colloidal anhydrous silica

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E171)
Red iron oxide (E172)
Black iron oxide (E172)
Talc
Soya lecithin
Xanthan gum

Mayzent 1 mg film-coated tablets

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Crospovidone
Glycerol dibehenate
Colloidal anhydrous silica

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E171)
Red iron oxide (E172)
Black iron oxide (E172)
Talc
Soya lecithin
Xanthan gum

Mayzent 2 mg film-coated tablets

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Crospovidone
Glycerol dibehenate
Colloidal anhydrous silica

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)
Talc
Soya lecithin
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

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 in wallet.
Packs of 84 or 120 film-coated tablets in PA/alu/PVC/alu blisters.

Mayzent 1 mg film-coated tablets

Packs of 28 or 98 film-coated tablets in PA/alu/PVC/alu blisters.

Mayzent 2 mg film-coated tablets

Packs of 14, 28 or 98 film-coated tablets in PA/alu/PVC/alu blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Mayzent 0.25 mg film-coated tablets

EU/1/19/1414/001
EU/1/19/1414/002
EU/1/19/1414/004

Mayzent 1 mg film-coated tablets

EU/1/19/1414/007
EU/1/19/1414/008

Mayzent 2 mg film-coated tablets

EU/1/19/1414/003
EU/1/19/1414/005
EU/1/19/1414/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 January 2020
Date of latest renewal: 19 September 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
1000 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Mayzent in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where Mayzent is marketed, all physicians who intend to prescribe Mayzent are provided with an updated Physician Education Pack, including:
- Summary of Product Characteristics;
- Physician's Checklist to consider prior to prescribing Mayzent;
- Patient/Caregiver Guide to be provided to all patients;
- Pregnancy Reminder Card for women of childbearing potential.

Physician's Checklist:

The Physician's Checklist shall contain the following key messages:

- Potential long-term safety implications in CYP2C9 poor metabolisers:
  - Perform genotyping for CYP2C9 before treatment initiation to determine the siponimod maintenance dose. Test requires a DNA sample obtained via blood or saliva (buccal swab). The test identifies two variant alleles for CYP2C9: CYP2C9*2 (rs1799853, c.430C>T) and CYP2C9*3 (rs1057910, c.1075A>C). Both are single nucleotide polymorphisms. This genotyping can be done using a Sanger sequencing method or PCR-based assay methods. For further clarifications please refer to your local laboratory.
  - Do not prescribe siponimod in patients homozygous for CYP2C9*3*3.
  - Adjust the maintenance dose to 1 mg in patients with CYP2C9*2*3 or *1*3 genotypes.

- Bradyarrhythmia (including conduction defects) during treatment initiation:
  - Initiate treatment with a titration pack that lasts for 5 days. Start treatment with 0.25 mg on day 1, up-titrated to the maintenance dose of 2 mg or 1 mg on day 6 based on the CYP2C9 metaboliser status.
  - If a titration dose is missed on one day during the first 6 days of treatment, treatment must be re-initiated with a new titration pack.
  - If the maintenance dose is interrupted for 4 or more consecutive daily doses, treatment must be re-initiated with a new titration pack.
  - Monitoring requirements at treatment initiation:
    Prior to initiating treatment:
    - Perform vitals and baseline ECG prior to the first dose of siponimod in patients with sinus bradycardia (heart rate [HR] <55 bpm), history of first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure (patients with NYHA class I and II).

    Until 6 hours after first dose:
    - Observe patients with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (patients with NYHA class I and II) for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia and obtain an ECG at the end of the 6-hour monitoring period.
    - If necessary, the decrease in heart rate induced by siponimod can be reversed by parenteral doses of atropine or isoprenaline.

    Extended observation (>6 hours after first dose):
    - If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/re-initiation. Repeat the first-dose monitoring after the second dose of siponimod.
- Appropriate management should be initiated and observation continued until the symptoms/findings have resolved if the following events are observed:
  a. New onset third-degree AV block occurring at any time
  b. Where at the 6-hour time point the ECG shows: New onset second-degree or higher AV block, or QTc interval ≥500 msec

  If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose.

- Mayzent is contraindicated in:
  - Patients who, in the previous 6 months, had a myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring in-patient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
  - Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick sinus syndrome, if they do not wear a pacemaker.
- Mayzent is not recommended in:
  - Patients with the below conditions. Siponimod treatment should be considered in these patients only if the anticipated benefits outweigh the potential risks and a cardiologist must be consulted to determine appropriate monitoring. At least overnight extended monitoring is recommended.
    - QTc prolongation >500 msec
    - Severe untreated sleep apnoea
    - History of symptomatic bradycardia
    - History of recurrent syncope
    - Uncontrolled hypertension
    - Concomitant treatment with class Ia (e.g. quinidine, procainamide) or class III anti-arrhythmic medicines, calcium channel blockers (such as verapamil, diltiazem) and other medicines (e.g. ivabradine or digoxin) which are known to decrease the heart rate

- Infections, including varicella zoster reactivation, reactivation of the other viral infections, PML and other rare opportunistic infections:
  - There is an increased risk of infections including serious infections, in patients treated with siponimod.
  - Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended 3 to 4 months after treatment initiation and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte counts $<0.2 \times 10^9$/l, if confirmed, should lead to dose reduction to 1 mg, because in clinical studies siponimod 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 siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches 0.6×10^9/l when re-initiation of siponimod can be considered.
  - Before starting siponimod, test for antibodies to varicella zoster virus (VZV) in patients without a physician-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If tested negative, vaccination is recommended and treatment with siponimod should be postponed for 1 month to allow the full effect of vaccination to occur.
  - Siponimod is contraindicated in patients with immunodeficiency syndrome.
  - Siponimod is contraindicated in patients with history of progressive multifocal leukoencephalopathy or cryptococcal meningitis.

- Do not initiate siponimod treatment in patients with severe active infection until infection is resolved.
- Exercise caution when administering concomitant treatment with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) due to the risk of additive immune system effects.
- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to one month after treatment with siponimod.
- Monitor patients carefully for signs and symptoms of infections during and after treatment with siponimod:
    - Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; siponimod treatment should be suspended until exclusion; appropriate treatment of infection, if diagnosed, should be initiated.
    - Cases of herpes viral infection (including cases of meningitis or meningoencephalitis caused by varicella zoster viruses) have occurred with siponimod at any time during treatment.
    - Cases of cryptococcal meningitis (CM) have been reported for siponimod.
    - Cases of progressive multifocal leukoencephalopathy (PML) have been reported for S1P receptor modulators, including siponimod, and other therapies for multiple sclerosis. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with siponimod should be suspended until PML has been excluded. If PML is confirmed, treatment with siponimod should be discontinued.
    - Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptor modulators, including siponimod, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

- <u>Macular oedema:</u>
    - Arrange an ophthalmological evaluation prior to initiating therapy and follow-up evaluations while receiving therapy in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease.
    - An ophthalmological evaluation 3-4 months after treatment initiation with siponimod is recommended.
    - Instruct the patient to report visual disturbances at any time while on siponimod therapy.
    - Do not initiate siponimod treatment in patients with macular oedema until resolution.

- <u>Reproductive toxicity:</u>
    - Siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Advise women of potential serious risks to the foetus if siponimod is used during pregnancy or if the patient becomes pregnant while taking it.
    - A negative pregnancy test result is required prior to initiation of treatment in women of childbearing potential and must be repeated at suitable intervals.
    - Women of childbearing potential should be counselled before treatment initiation and regularly thereafter about the serious risks of siponimod to the foetus, facilitated by the pregnancy-specific patient reminder card.
    - Women of childbearing potential must use effective contraception during treatment and for at least 10 days following discontinuation of treatment with siponimod.
    - Siponimod should be stopped at least 10 days before a pregnancy is planned. When stopping siponimod for planning a pregnancy the possible return of disease activity should be considered.
    - Counsel the patient in case of inadvertent pregnancy.

- If a woman becomes pregnant while on treatment with siponimod, treatment must be discontinued. Pregnant women should be advised of potential serious risks to the foetus, and ultrasonography examinations should be performed.
- Should a pregnancy occur during treatment or within 10 days following discontinuation of treatment with siponimod, please report it to Novartis by calling [insert local number] or visiting [insert URL], irrespective of adverse outcomes observed.
- Novartis has put in place a PRegnancy outcomes Intensive Monitoring (PRIM) programme, which is a registry based on enhanced follow-up mechanisms to collect information about pregnancy in patients exposed to siponimod immediately before or during pregnancy and on infant outcomes 12 months post-delivery.

- Other reminders:
  - Perform liver function tests prior to initiating siponimod treatment. If patients develop symptoms suggestive of hepatic dysfunction during treatment with siponimod, request a liver enzymes check. Discontinue treatment if significant liver injury is confirmed. Siponimod is contraindicated in patients with severe liver impairment (Child-Pugh class C).
  - Be vigilant for skin malignancies while on treatment with siponimod. Perform skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. Siponimod is contraindicated in patients with active malignancies.
  - Should a patient develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled and MRI should be considered.
  - Caution should be exercised in elderly patients with multiple co-morbidities, or advanced disease/disability (due to possible increased risks of, for example, infections, bradyarrhythmic events during treatment initiation).
  - If siponimod is discontinued, the possibility of recurrence of high disease activity should be considered.
  - Provide patients with the Patient/Caregiver Guide and Pregnancy Reminder Card for women of childbearing potential.
  - Be familiar with the Mayzent Prescribing Information.

Patient/Caregiver Guide:

The Patient/Caregiver Guide shall contain the following key messages:

- What Mayzent is and how it works.
- What multiple sclerosis is.
- Patients should read the package leaflet thoroughly before starting treatment and should keep the package leaflet in case they need to refer to it again during treatment.
- The importance of reporting adverse reactions.
- Before starting treatment, a DNA sample via blood or saliva (buccal swab) is taken to determine the CYP2C9 genotype to help determine appropriate dosing of siponimod. In certain cases the patient may not receive treatment with siponimod due to specific CYP2C9 genotype status.
- Patients need to have chickenpox vaccination 1 month before starting siponimod treatment, if the patient is not protected against the virus.
- Siponimod is not recommended in patients with cardiac disease or taking concomitant medicines known to decrease heart rate. Patients should tell any doctor they see that they are being treated with siponimod.

- For patients with certain heart problems, an ECG before initiating treatment with siponimod will be needed. The need for observation (including an ECG monitoring) for 6 hours in a clinic after the first dose of siponimod on day 1, if the patient has heart problems. Information that the monitoring may need to extend overnight, if the patient experiences symptoms during the first 6 hours.
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of siponimod and during the titration period.
- Before starting treatment patients should provide a recent complete blood count. Assessments of CBC are also recommended 3 to 4 months after treatment initiation and at least yearly thereafter, and in case of signs of infection.
- The signs and symptoms of infection during, and up to one month after treatment with siponimod need to be reported immediately to the prescriber, including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, caused by either a fungal or viral infection).
    - If you believe your MS is getting worse or if you notice any new symptoms during and after treatment with Mayzent, for example changes in mood or behaviour, new or worsening weakness on one side of the body, changes in vision, confusion, memory lapses or speech and communication difficulties. These may be symptoms of PML or of an inflammatory reaction (known as immune reconstitution inflammatory syndrome or IRIS) that can occur in patients with PML as Mayzent is removed from their body after they stop taking it.
- Patients should report any symptoms of visual impairment immediately to the prescriber during and for up to one month after the end of treatment with siponimod.
- Patients should call the doctor if a dose is missed during the first 6 days of treatment or for 4 or more consecutive days after initiating treatment with siponimod. Treatment needs to be reinitiated with a new titration pack.
- Liver function tests should be performed before starting treatment and repeated if there are symptoms suggestive of hepatic dysfunction.
- Patients should report any unexpected neurological or psychiatric symptoms/signs (such as sudden onset of severe headache, confusion, seizures and vision changes) or accelerated neurological deterioration to their doctors.
- Due to the potential teratogenic risk of siponimod women of childbearing potential should:
    - Be informed before treatment initiation and regularly thereafter by their physician about siponimod serious risks to the foetus and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the Pregnancy Reminder Card.
    - Have a negative pregnancy test before starting siponimod, which should be repeated at suitable intervals.
    - Be using effective contraception during treatment and for at least 10 days after stopping treatment to avoid pregnancy due to the potential risk of harm to the unborn baby.
    - Report immediately to the prescribing physician any (intended or unintended) pregnancy, during treatment and up to 10 days following discontinuation of siponimod treatment.
- Patients should be informed about the risk of skin malignancies and the need for skin examinations at the start of the treatment and thereafter while on treatment with siponimod. Patients should be cautioned against exposure to sunlight without protection. Also, patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. Patients should inform their doctor immediately if they notice any skin nodules (e.g. shiny, pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g. unusual moles) with a change in colour, shape or size over time.
- After stopping treatment with Mayzent, patients should inform their doctor immediately if their disease symptoms are getting worse (e.g. weakness or visual changes) or if they notice any new symptoms.
- Contact details of the siponimod prescriber.

Pregnancy Reminder Card for women of childbearing potential:

The pregnancy-specific patient reminder card shall contain the following key messages:

- Siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Patients should inform their doctor immediately if they think they are pregnant. Doctors will provide counselling before treatment initiation and regularly thereafter regarding the potential teratogenic risk of siponimod and required actions to minimise this risk.
- Patients will be informed by their doctor of the need for effective contraception while on treatment and for 10 days after discontinuation.
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals.
- Patients must use effective contraception during the treatment with siponimod.
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, siponimod should be discontinued. Effective contraception should be maintained for at least 10 days following discontinuation of treatment with siponimod.
- Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with siponimod.
- Women exposed to siponimod during pregnancy are encouraged to join the pregnancy exposure programme (PRegnancy outcomes Intensive Monitoring, PRIM) that monitors outcomes of pregnancy.
- Should a pregnancy occur during treatment or within 10 days following discontinuation of treatment with siponimod, it should be immediately reported to the doctor or to Novartis by calling [insert local number] or visiting [insert URL], irrespective of adverse outcomes observed.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 0.25 mg film-coated tablets
siponimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.25 mg siponimod (as fumaric acid).

3. LIST OF EXCIPIENTS

Contains lactose and soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Titration pack
12 film-coated tablets
84 film-coated tablets
120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1414/001	Titration pack of 12 film-coated tablets
EU/1/19/1414/002	120 film-coated tablets
EU/1/19/1414/004	84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mayzent 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INNER PACKAGING

WALLET CONTAINING BLISTER (titration pack of 12 film-coated tablets of 0.25 mg)

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 0.25 mg film-coated tablets
siponimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.25 mg siponimod (as fumaric acid).

3. LIST OF EXCIPIENTS

Contains lactose and soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Titration pack
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Take tablet(s) at the same time every day.
Start
Day 1
Day 2
Day 3
Day 4
Day 5

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1414/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (packs of 84 and 120 film-coated tablets of 0.25 mg)

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 0.25 mg film-coated tablets
siponimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 1 mg film-coated tablets
siponimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg siponimod (as fumaric acid).

3. LIST OF EXCIPIENTS

Contains lactose and soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1414/007	28 film-coated tablets
EU/1/19/1414/008	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mayzent 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 1 mg film-coated tablets
siponimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.
Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 2 mg film-coated tablets
siponimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg siponimod (as fumaric acid).

3. LIST OF EXCIPIENTS

Contains lactose and soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1414/003	28 film-coated tablets
EU/1/19/1414/005	14 film-coated tablets
EU/1/19/1414/006	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mayzent 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Mayzent 2 mg film-coated tablets
siponimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.
Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mayzent 0.25 mg film-coated tablets
Mayzent 1 mg film-coated tablets
Mayzent 2 mg film-coated tablets
siponimod

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mayzent is and what it is used for
2. What you need to know before you take Mayzent
3. How to take Mayzent
4. Possible side effects
5. How to store Mayzent
6. Contents of the pack and other information

1. What Mayzent is and what it is used for

What Mayzent is
Mayzent contains the active substance siponimod. Siponimod belongs to a group of medicines called sphingosine-1-phosphate (S1P) receptor modulators.

What Mayzent is used for
Mayzent is used to treat adults with secondary progressive multiple sclerosis (SPMS) with active disease. Active disease in SPMS is when there are still relapses or when MRI (magnetic resonance imaging) results show signs of inflammation.

How Mayzent works
Mayzent helps to protect the central nervous system (CNS) from attacks by the body's own immune system. It does this by:
- making some white blood cells (called lymphocytes) less able to move freely within the body, and
- stopping these cells from reaching the brain and spinal cord.

This reduces nerve damage caused by SPMS and as a result Mayzent helps to slow down the effects of the disease activity (such as worsening disability, brain lesions and relapses).

2. What you need to know before you take Mayzent

Do not take Mayzent
- if you are allergic to siponimod, peanut, soya or any of the other ingredients of this medicine (listed in section 6).
- if you have an immunodeficiency syndrome.
- if you have ever had progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- if you have an active cancer.
- if you have severe liver problems.

- if, in the last 6 months, you have had a heart attack, unstable angina, stroke or certain types of heart failure.
- if you have certain types of irregular or abnormal heartbeat (arrhythmia) and you do not have a pacemaker.
- if blood tests show that your body cannot break down this medicine well enough, you should not take it (see "Blood tests before and during treatment" below).
- if you are pregnant or could become pregnant and are not using effective contraception.

Warnings and precautions
Talk to your doctor **before** taking Mayzent:
- if you have an infection or if your immune system does not work properly (for example due to a disease or to medicines that suppress the immune system; see also "Other medicines and Mayzent").
- if you have never had chickenpox and have not been vaccinated against it. You may be at greater risk of complications if you develop chickenpox during Mayzent treatment. Your doctor may want to vaccinate you against chickenpox before you start treatment.
- if you are planning to have any vaccinations. Your doctor will advise you on this (see "Other medicines and Mayzent").
- if you have ever had, or have, difficulties with your vision (in particular a condition called macular oedema) or an infection or inflammation of the eye (uveitis). Your doctor may want you to have eye examinations before you start treatment and regularly while you are on treatment. Mayzent can cause a swelling in the macula (the area of the eye that enables you to see shapes, colours and details) known as macular oedema. Your chance of developing macular oedema is higher if you have had it before or if you have ever had uveitis (an inflammation of the eye).
- if you have diabetes. The chance of developing macular oedema (see above) is higher in patients with diabetes.
- if you have ever had any of the following conditions (even if you are receiving treatment for them): severe heart disease, irregular or abnormal heartbeat (arrhythmia), stroke or other disease related to the blood vessels in the brain, a slow heart rate, fainting, disturbance of heart rhythm (indicated by abnormal ECG results).
- if you have severe breathing problems when sleeping (sleep apnoea).
- if you have high blood pressure that cannot be controlled by medicines. Your blood pressure will need to be checked regularly.
- if you have ever had liver problems. Your doctor may want to perform blood tests to check your liver function before prescribing Mayzent.
- if you could become pregnant, because siponimod can harm the unborn baby when used during pregnancy. Before you start treatment, your doctor will explain the risk and ask you to do a pregnancy test to ensure that you are not pregnant. You must use effective contraception during treatment and for at least 10 days after stopping treatment (see "Pregnancy, breast-feeding and fertility").

If any of the above applies to you, tell your doctor **before** taking Mayzent.

Look out for the following while taking Mayzent
If you get any of the following while taking Mayzent, **tell your doctor immediately** because it could be serious:
- if you have an infection. Mayzent lowers the number of white cells in your blood. White blood cells fight infection, so you may get infections more easily while you are taking Mayzent (and up to 3 to 4 weeks after you stop taking it). These could be serious and possibly even life-threatening.

- if you think your multiple sclerosis (MS) is getting worse or if you notice any new or unusual symptoms. A rare brain infection called progressive multifocal leukoencephalopathy (PML) can cause symptoms similar to SPMS. It can occur in patients taking medicines like Mayzent and other medicines used for treating MS. If PML is confirmed, your doctor will stop treatment with Mayzent. Some people can get a reaction as Mayzent is removed from the body. This reaction (known as immune reconstitution inflammatory syndrome or IRIS) may lead to your condition getting worse, including worsening of brain function.
- if you have fever, feel like you have flu or have a headache together with a stiff neck, sensitivity to light, nausea or confusion. These may be symptoms of meningitis and/or encephalitis caused by a viral or fungal infection (such as cryptococcal meningitis).
- if you have changes in your vision, for example if the centre of your vision becomes blurred or has shadows, a blind spot develops in the centre of your vision, or you have problems seeing colours or fine detail. These may be symptoms of macular oedema. You may not notice any symptoms in the early stages of macular oedema, and it can cause some of the same visual symptoms as an MS attack (optic neuritis). Your doctor may want you to have an eye examination 3 or 4 months after starting treatment and possibly again later. If macular oedema is confirmed, your doctor may advise you to stop Mayzent treatment.
- if you have symptoms such as sudden onset of severe headache, confusion, seizures and vision changes. These may be symptoms of a condition called posterior reversible encephalopathy syndrome (PRES).
- if you have symptoms such as unexplained nausea, vomiting, abdominal pain, tiredness, yellowing of the skin or whites of the eyes or abnormally dark urine. These may be symptoms of liver problems.
- if you notice any skin nodules (e.g. shiny, pearly nodules), patches or open sores that do not heal within weeks.

Slow heart rate (bradycardia) and irregular heartbeat
During the first days of treatment, Mayzent can cause the heart rate to slow down (bradycardia). You may not feel anything or you may feel dizzy or tired. It may also cause your heartbeat to become irregular at the beginning of treatment. If anything indicates that you may be at higher risk of suffering from these effects, your doctor may decide to monitor you more closely at the start of treatment, refer you first to a heart specialist (cardiologist), or choose not to give you Mayzent.

Tests before and during treatment
How quickly this medicine is broken down (metabolised) in the body varies from patient to patient and different people therefore require different doses. Your doctor will perform a blood or saliva test before you start treatment to determine which dose is best for you. In rare cases, the test result may indicate that you should not take Mayzent.

- **Blood count**

The desired effect of Mayzent treatment is to reduce the amount of white blood cells in your blood. This will usually go back to normal within 3-4 weeks of stopping treatment. If you need to have any blood tests, tell the doctor that you are taking Mayzent. Otherwise, it may not be possible for the doctor to understand the results of the test, and for certain types of blood test your doctor may need to take more blood than usual.

Before you start Mayzent, your doctor will confirm whether you have enough white blood cells in your blood and may want to repeat a check regularly. In case you do not have enough white blood cells, your doctor may need to stop or reduce your Mayzent dose.

Before the start of treatment your blood will also be tested to check how well your liver is working.

Skin cancer
Skin cancers have been reported in MS patients treated with Mayzent. Talk to your doctor straight away if you notice any skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g. unusual moles) with a change in colour, shape or size over time. Before you start Mayzent, a skin examination is required to check whether you have any skin nodules. Your doctor will also carry out regular skin examinations during your treatment with Mayzent. If you develop problems with your skin, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis.

Exposure to the sun and protection against the sun
Mayzent weakens your immune system. This may increase your risk of developing skin cancer. You should limit your exposure to the sun and UV rays by:
- wearing appropriate protective clothing.
- regularly applying sunscreen with a high degree of UV protection.

Worsening of MS after stopping Mayzent treatment
Do not stop taking Mayzent or change your dose without talking to your doctor first.

Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Mayzent (see "If you stop taking Mayzent" in section 3).

Elderly patients (65 years of age and above)
There is no experience with Mayzent in elderly patients. Talk to your doctor if you have any concerns.

Children and adolescents
Do not give this medicine to children and adolescents below 18 years of age because it has not yet been studied in this age group.

Other medicines and Mayzent
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Make sure to tell your doctor if you are taking or receiving any of the following medicines or therapies:
- medicines for an irregular heartbeat, such as amiodarone, procainamide, quinidine or sotalol. Your doctor may decide not to prescribe Mayzent because it could intensify the effect on irregular heartbeat.
- medicines that slow down the heartbeat, such as diltiazem or verapamil (which belong to a group of medicines called calcium channel blockers), digoxin or ivabradine. Your doctor may refer you to a heart specialist, as your medicines may need to be changed because Mayzent may also slow down your heartbeat in the first days of treatment. If you are taking a beta blocker, such as atenolol or propranolol, your doctor may ask you to temporarily stop your beta-blocker treatment until you have reached your full daily dose of Mayzent.
- medicines that affect the immune system, such as chemotherapy, immunosuppressants or other medicines to treat MS. Your doctor may ask you to stop taking these to avoid an increased effect on the immune system.
- vaccines. If you need to have a vaccination, talk to your doctor first. During and for 4 weeks after stopping treatment with Mayzent, you should not be given certain types of vaccine (called live attenuated vaccines) as they could trigger the infection that they were supposed to prevent (see section 2).
- strong CYP2C9 inhibitors are anticipated to increase the levels of Mayzent in the blood and are not recommended to be taken in combination with Mayzent. Your doctor will advise you on this.
- carbamazepine and certain other medicines can lower the levels of Mayzent in your blood and can therefore stop it from working properly. Your doctor will advise you on this.
- modafinil and certain other medicines can lower the levels of Mayzent in the blood of certain patients and can therefore stop it from working properly. Your doctor will advise you on this if this is relevant for you.

- phototherapy with UV radiation or PUVA photochemotherapy. UV therapy during Mayzent treatment may increase your risk of developing skin cancer.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.

Do not use Mayzent during pregnancy, if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception. If Mayzent is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk before you start treatment with Mayzent and will ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Mayzent and for at least 10 days after you stop taking it to avoid becoming pregnant. Ask your doctor about reliable methods of contraception.

If you do become pregnant while taking Mayzent, tell your doctor straight away. Your doctor will decide to stop treatment (see "If you stop taking Mayzent" in section 3). Specialised pre-natal monitoring will be performed.

You should not breast-feed while you are taking Mayzent. Mayzent may pass into breast milk and there is a risk of serious side effects for the baby.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Mayzent is not expected to affect your ability to drive and use machines when you are on your regular treatment dose. At the start of treatment you may occasionally feel dizzy. On your first day of treatment with Mayzent, therefore, you should not drive or use machines.

Mayzent contains lactose and soya lecithin
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

If you are allergic to peanut or soya, do not use this medicine.

3. How to take Mayzent

Treatment with Mayzent will be overseen by a doctor who is experienced in the treatment of MS.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How much Mayzent to take
Starting treatment
You will be given a titration pack, with which your dose will be gradually increased over 5 days. Follow the instructions on the pack (see also the "Titration pack" table).

The purpose of the titration phase is to reduce the risk of side effects on your heart at the start of treatment. Your doctor may monitor you closely at the start of treatment if you are at risk of your heartbeat becoming slower or irregular.

Titration pack

Day	Dose	Number of Mayzent 0.25 mg tablets to take
Day 1	0.25 mg	1 tablet
Day 2	0.25 mg	1 tablet
Day 3	0.5 mg	2 tablets
Day 4	0.75 mg	3 tablets
Day 5	1.25 mg	5 tablets

On day 6, you will switch to your regular treatment dose.

On the first 6 days of treatment, it is recommended that you take the tablets in the morning with or without food.

Treatment dose
The recommended dose is 2 mg once daily (one tablet of 2 mg Mayzent) with or without food.

Your doctor may instruct you to take only 1 mg once daily (one tablet of Mayzent 1 mg or four tablets of Mayzent 0.25 mg) if the blood test performed before the start of treatment showed that your body breaks down Mayzent slowly (see "Tests before and during treatment"). If this applies to you, note that it is nevertheless safe for you to take five 0.25 mg tablets on day 5 of the titration period as indicated above.

Mayzent is for oral use. Take the tablet with water.

If you take more Mayzent than you should
If you have taken too many Mayzent tablets, or if you take your first tablet from the treatment dose pack instead of the titration pack by mistake, call your doctor straight away. Your doctor may decide to keep you under observation.

If you forget to take Mayzent
During the first 6 days of treatment, if you have forgotten to take your dose on one day, call your doctor before you take the next dose. Your doctor will need to prescribe a new titration pack. You will have to restart at day 1.

If you miss a dose when you are on the regular treatment dose (day 7 onwards), take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. If you forget to take Mayzent for 4 or more days in a row, call your doctor before you take the next dose. Your doctor will need to prescribe a new titration pack and you will have to restart treatment at day 1.

If you stop taking Mayzent
Do not stop taking Mayzent or change your dose without talking to your doctor first.

Mayzent will stay in your body for up to 10 days after you stop taking it. Your white blood cell (lymphocyte) count may remain low for up to 3 to 4 weeks after you stop taking Mayzent. The side effects described in this leaflet may still occur during this period (see "Possible side effects" in section 4).

If you have to restart Mayzent more than 4 days after you stopped taking it, your doctor will prescribe a new titration pack and you will have to restart treatment at day 1 again.

Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Mayzent.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Common (may affect up to 1 in 10 people)

- Rash with small fluid-filled blisters, appearing on reddened skin (symptoms of a viral infection called herpes zoster that can be severe)
- A type of skin cancer called basal cell carcinoma (BCC) which often appears as a pearly nodule, though it can also take other forms.
- Fever, sore throat and/or mouth ulcers due to infection (lymphopenia)
- Convulsions, fits
- Visual disturbances such as a shadow or a blind spot in the centre of vision, blurred vision, problems seeing colours or details (symptoms of macular oedema, which is a swelling in the macular area of the retina at the back of the eye)
- Irregular heartbeat (atrioventricular block)
- Slow heartbeat (bradycardia)

Uncommon (may affect up to 1 in 100 people)

- A type of skin cancer called squamous cell carcinoma which may present as a firm red nodule, a sore with a crust, or a new sore on an existing scar
- A type of skin cancer called malignant melanoma which usually develops from an unusual mole. Possible signs of melanoma include moles which may change size, shape, elevation or colour over time, or new moles. The moles may itch, bleed or ulcerate.

Rare (may affect up to 1 in 1 000 people)

- A brain infection called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to MS such as weakness or visual changes, memory loss, trouble thinking or difficulty walking.
- Inflammatory disorder after stopping Mayzent treatment (known as immune reconstitution inflammatory syndrome or IRIS).

Not known (frequency cannot be estimated from the available data)

- Cryptococcal infections (a type of fungal infection) or viral infections (caused by herpes or varicella zoster virus), including meningitis and/or encephalitis with symptoms such as headache together with stiff neck, sensitivity to light, feeling sick (nausea) or confusion
- Allergic reactions, including symptoms of rash or itchy hives, swelling of lips, tongue or face.

If you get any of these, **tell your doctor straight away**.

Other side effects

Other side effects include those listed below. If any of these side effects becomes severe, **tell your doctor or pharmacist**.

Very common (may affect more than 1 in 10 people)

- headache
- high blood pressure (hypertension), sometimes with symptoms such as headache and dizziness
- blood test results showing increased liver enzyme levels

Common (may affect up to 1 in 10 people)

- new moles
- dizziness
- involuntary shaking of the body (tremor)
- diarrhoea

- feeling sick (nausea)
- pain in hands or feet
- swollen hands, ankles, legs or feet (peripheral oedema)
- weakness (asthenia)
- lung function test results showing decreased function

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mayzent

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton/blister foil after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mayzent contains
- The active substance is siponimod.

Mayzent 0.25 mg film-coated tablets
- Each tablet contains 0.25 mg siponimod (as siponimod fumaric acid).
- The other ingredients are:
  Tablet core: Lactose monohydrate (see "Mayzent contains lactose and soya lecithin" in section 2), microcrystalline cellulose, crospovidone, glycerol dibehenate, colloidal anhydrous silica.
  Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172), talc, soya lecithin (see "Mayzent contains lactose and soya lecithin" in section 2), xanthan gum.

Mayzent 1 mg film-coated tablets
- Each tablet contains 1 mg siponimod (as siponimod fumaric acid).
- The other ingredients are:
  Tablet core: Lactose monohydrate (see "Mayzent contains lactose and soya lecithin" in section 2), microcrystalline cellulose, crospovidone, glycerol dibehenate, colloidal anhydrous silica.
  Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172), talc, soya lecithin (see "Mayzent contains lactose and soya lecithin" in section 2), xanthan gum.

Mayzent 2 mg film-coated tablets

- Each tablet contains 2 mg siponimod (as siponimod fumaric acid).
- The other ingredients are:
  Tablet core: Lactose monohydrate (see "Mayzent contains lactose and soya lecithin" in section 2), microcrystalline cellulose, crospovidone, glycerol dibehenate, colloidal anhydrous silica.
  Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), talc, soya lecithin (see "Mayzent contains lactose and soya lecithin" in section 2), xanthan gum.

What Mayzent looks like and contents of the pack
Mayzent 0.25 mg film-coated tablets are pale red, round film-coated tablets with the company logo on one side and "T" on the other side.

Mayzent 1 mg film-coated tablets are violet white, round film-coated tablets with the company logo on one side and "L" on the other side.

Mayzent 2 mg film-coated tablets are pale yellow, round film-coated tablets with the company logo on one side and "II" on the other side.

Mayzent 0.25 mg film-coated tablets are available in the following pack sizes:

- Titration pack as wallet containing 12 tablets, and
- Packs containing 84 or 120 tablets

Mayzent 1 mg film-coated tablets are available in packs containing 28 or 98 tablets.

Mayzent 2 mg film-coated tablets are available in packs containing 14, 28 or 98 tablets.

Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.