Regulatory Affairs

Mayzent®

Summary of the Local Safety Risk Management Plan

Active substance(s) (INN or common name):	*Siponimod*
Product(s) concerned (brand name(s)):	*Mayzent*
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Summary of the risk management plan for Mayzent (Siponimod)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Mayzent is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Mayzent in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Mayzent.

I. The medicine and what it is used for

Siponimod 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. It contains siponimod as the active substance and it is given as 0.25 mg and 2 mg film-coated tablets.

Further information about the evaluation of siponimod's benefits can be found in siponimod EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of siponimod, together with measures to minimize such risks and the proposed studies for learning more about siponimod's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use including treatment adherence, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of siponimod, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of siponimod is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of siponimod are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of siponimod. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

Important identified risks	• Varicella-zoster virus (VZV) Infection reactivation • Cryptococcal meningitis • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Basal cell carcinoma (BCC)
Important potential risks	• Potential long-term safety implications in CYP2C9 poor metabolizers • Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis • Thromboembolic events • Malignancies (excluding BCC) • Reproductive toxicity • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)
Missing information	• Safety in patients over 60 years old (including elderly) • Use during lactation • Long-term safety risks

II B: Summary of important risks

Table 13-2 Important identified risk: Varicella-zoster virus (VZV) Infection reactivation

Evidence for linking the risk to the medicine	Given the biologic plausibility and the well-characterized risk of infections with the other S1P modulator, infections are not unexpected. In the controlled pool, reactivation of VZV infection was reported for a higher percentage of siponimod 2 mg patients vs. placebo, but incidences were low (2.9% of siponimod 2 mg patients and 0.7% of placebo patients). The exposure adjusted rate of VZV reactivation did not increase with long-term exposure (IR: 1.7, 95% CI: 1.4, 2.2, for Long-term pool (broad) vs IR: 1.9 95% CI 1.3, 2.7 for the Controlled pool).

	In the Phase 3 study, decrease in lymphocyte count observed in patients in the siponimod 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues siponimod therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase 3 PopPKPD]. There was no increase in the number of infections following siponimod treatment compared to placebo, or with increasing average siponimod steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of herpes viral infections, opportunistic infections (includes cryptococcal infections) and PML were observed while on treatment with another S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported with the use of fingolimod, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL section 4 (possible side effects). SmPC section 4.3 includes following contraindications: Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC section 4.4 includes following recommendations: • Prior to Siponimod treatment initiation, • Test for varicella zoster virus (VZV) antibody in patients without physician confirmed or undocumented full course vaccination against VZV. • Provide varicella vaccination for antibody-negative patients. • Obtain a recent complete blood count (within last 6 months or after discontinuation of prior therapy). • Delay the Siponimod treatment in patients with severe active infection until resolution. • Vigilance for infection during Siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. • Stop Siponimod treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Siponimod therapy.

	• Exercise caution when Siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Siponimod treatment and for 4 weeks after stopping the Siponimod treatment. **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers - HCP checklist - Patient/Caregiver Guide
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-3 Important identified risk: Cryptococcal meningitis

Evidence for linking the risk to the medicine	Given the biologic plausibility and the well-characterized risk of infections with another S1P modulator, infections are not unexpected. A confirmed (positive CSF Gram stain and culture) case of cryptococcal (*C. neoformans*) meningitis was reported in a 62-year old patient participating in the extension part of the clinical trial, BAF312A2304, after approximately 2.5 years of Siponimod treatment at the dose of 2 mg/day. The patient no history of HIV/AIDS, recent high dose steroid/immunosuppressant use or exposure to birds. The patient completely recovered from the event after receiving appropriate treatment including anti-fungal medications. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase 3 PopPKPD]. There was no increase in the number of infections following siponimod treatment compared to placebo, or with increasing average siponimod steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of herpes viral infections, opportunistic infections (includes cryptococcal infections) and PML were observed while on treatment with another S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported with the use of fingolimod, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at an increased risk of cryptococcal infections.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL section 4 (possible side effects). SmPC section 4.3 includes following contraindications:

	Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC section 4.4 includes following recommendations: • Patient with such symptoms and signs should undergo prompt diagnostic evaluation • The treatment with siponimod should be stopped until the diagnosis of CM has been excluded. • Appropriate treatment should be initiated, if CM is diagnosed **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers - HCP checklist - Patient/Caregiver Guide
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-4 Important identified risk: Bradyarrhythmia (including conduction defects) during treatment initiation

Evidence for linking the risk to the medicine	In the Clinical Pharmacology studies, (single doses up to 75 mg, multiple doses up to 20 mg qd) and studies in PM/DM patients (highest dose 10 mg qd), a dose-dependent decrease in mean heart rate was observed over the first 24 h post-dose, plateauing at doses of 5 mg and above. Decreases in heart rate were transient and peaked approximately 2 h post-dose for all doses. In Study A2201, when siponimod was started without dose titration in the maintained dose of 2 mg or 10 mg five transient symptomatic bradyarrhythmic events were observed on Day 1. The events resolved without sequelae after drug discontinuation. Other findings included dose dependent, transient decrease in heart rate on Day 1 with the maximum decreases observed 2 hours post first dose (mean change of app. 10 bpm for 10 mg dose) in Period 1 of the study. Based upon these observations, dose titration was implemented in Study A2201 in Period 2. Following the introduction of the initial-dose titration scheme, there were no symptomatic bradyarrhythmic events or AV-blocks of concern. In Study A2304, the targeted maintenance dose of 2 mg of siponimod was reached through 6 days of titration. In this study, the most prominent decreases in heart rate were observed on Day 1, 4 hours post dose (mean decreases of 5.30 bpm in siponimod and 0.76 bpm in placebo group); in general 5.9% of siponimod patients were observed with HR <50 bpm compared with 1.2% of placebo patients. During the titration period for the combined terms of bradyarrhythmia and bradycardia, 7.4% of patients in the siponimod group and 2.9% of placebo group had events, transient and mostly asymptomatic. Discontinuation due to first or second degree AV block was reported in 0.2% siponimod (2 first degree AV block and 2 second degree AV Mobitz type I; one patient experienced both) and none in placebo patients (A2304).
Risk factors and risk groups	Patients with underlying medical history and/or receiving co-medications that might increase the risk of bradycardia or in whom bradycardia may be poorly tolerated include:

	• second degree Mobitz type II or higher AV block, • sick-sinus syndrome • sino-atrial heart block, • history of symptomatic bradycardia or recurrent syncope, • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension • severe sleep apnea patients with significant QT prolongation (QTc >500 msec) • Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, beta blockers, and heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects), PL section 4 (possible side effects). SmPC section 4.2 and PL section 3 included recommendation on initiating the treatment with titration pack and reinitiating treatment when a dose is missed during the first 6 days of treatment or missed doses for 4 or more consecutive daily doses during maintenance treatment. - Siponimod needs to be re-initiated with a new titration pack when a dose is missed on one day during the first 6 days of treatment or maintenance treatment is interrupted for 4 or more consecutive daily doses. SmPC section 4.3 includes following contraindications: • Patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or 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. SmPC section 4.4 includes following recommendations: Apply an up-titration scheme to reach the maintenance dose on day 6 at treatment start. 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, obtain an electrocardiogram (ECG) prior to dosing and at the end of the observation period. Use of Siponimod is not recommended in patients with the following cardiac conditions and in patients taking certain antiarrhythmic, heart-rate lowering medications during treatment initiation. If treatment with Siponimod is considered in these patients, it is recommended to seek

advice from a cardiologist for determining an appropriate strategy for siponimod treatment initiation monitoring or switching the treatment to a non-heart-rate lowering treatment.

- In patients with a history of uncontrolled hypertension or severe untreated sleep apnoea as significant bradycardia may be poorly tolerated in these patients.
- In patients with a history of recurrent syncope or symptomatic bradycardia.
- In patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties.
- In patients with Class Ia and class III antiarrhythmic medicinal products or with heart-rate-lowering calcium channel blockers, or other substances that may decrease heart rate.
- In patients with a resting heart rate ≤ 50 bpm under chronic beta-blocker treatment, beta-blocker treatment should be interrupted before treatment initiation with Siponimod. If resting heart rate is > 50 bpm siponimod treatment can be initiated and treatment with beta blocker can be re-initiated after siponimod has been up-titrated to the target maintenance dose.

SmPC Section 4.7 includes following recommendations for patients during treatment initiation

- As dizziness may occasionally occur when initiating therapy with siponimod, patients should not drive or use machines during the first day of treatment initiation with siponimod.

Pack size: Titration pack consists of 12 film-coated tablets of 0.25 mg dose in a wallet. The titration pack allows gradual increase of the dose over a period of 5 days. Titration ends on day 6 when the maintenance dose is reached. Titration minimizes the risk to experience symptomatic bradycardia or bradyarrhythmia.

Titration pack:

Titration	Titration dose	Titration regimen
Day 1	0.25 mg	1 tablet of 0.25 mg
Day 2	0.25 mg	1 tablet of 0.25 mg
Day 3	0.5 mg	2 tablets of 0.25 mg
Day 4	0.75 mg	3 tablets of 0.25 mg
Day 5	1.25 mg	5 tablets of 0.25 mg

Additional risk minimization measures:

Educational materials for HCPs and patients/care givers

- HCP checklist
- Patient/Caregiver Guide

Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-5 Important identified risk: Macular edema

Evidence for linking the risk to the medicine	Drug induced Macular edema has been reported with other S1P modulators. S1P modulators pharmacological action on the endothelial barrier function has been associated with incidence of macular edema. In the Controlled pool, macular edema (including cystoid macular edema) was reported as an AE in 20 (1.7%) siponimod 2 mg patients (Odds ratio of 10.7 vs Placebo 95% CI: 1.4, 80.3) and 1 (0.2%) placebo patient. There is no evidence of an increase in the incidence rate of macular edema over time [IR 0.6, per 100 PY (95% CI 0.4, 0.8) vs IR 1.2 (95% CI: 0.7, 1.8)] with siponimod treatment and the reported cases in the Long-term pool were consistent with the observations in the Controlled pool.
Risk factors and risk groups	Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal disorders are considered at increased risk of developing macular edema. Such patients should undergo an ophthalmic evaluation prior to initiating siponimod therapy and have follow-up evaluations while receiving siponimod therapy.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL section 4 (possible side effects). PL Section 2 included recommendation to monitor the symptoms of macular edema and to consult the physician for an ophthalmic examination. The SmPC section 4.4 included following recommendations: • An ophthalmic evaluation after 3 - 4 months of treatment initiation with Siponimod. • Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema. It is recommended that these patients undergo ophthalmic evaluation prior to the initiation and during the treatment with siponimod treatment. • As cases of macular edema have occurred on longer-term treatment, patients should report visual disturbances at any time while on Siponimod treatment and an evaluation of the fundus, including the macula is recommended. • It is recommended that siponimod be discontinued if a patient develops macular edema. 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. • Siponimod therapy should not be initiated in patients with macular oedema until resolution. **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers: - HCP checklist - Patient/Caregiver Guide

Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-6 Important identified risk: Basal Cell Carcinoma

Evidence for linking the risk to the medicine	Basal cell carcinoma has been reported for other S1P modulators. In study A2304, basal cell carcinoma was the most common neoplasm and was reported with a similiar incidence in the siponimod 2 mg (1.01%, 12 patients) and placebo (1.23%, 7 patients) groups. However, additional cases in patients treated with siponimod have been reported with longer exposure.
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects), PL section 4 (possible side effects). SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies SmPC Section 4.4 includes the following recommendations Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Patients should be advised to promptly report any suspicious skin lesions to their physician. These patients should be cautioned against exposure to sunlight without protection. These patients and they should not receive concomitant phototherapy with UV-B radiation or PUVA photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Additional risk minimization measures**: Educational material for HCPs and patients/care givers. - HCP checklist - Patient/Caregiver Guide
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part.

Table 13-7 Important potential risk: Potential long-term safety implications in CYP2C9 poor metabolizers

Evidence for linking the risk to the medicine	An exploratory PK/pharmacogenetic (PG) analysis in the first-in-human study indicated that heterozygous CYP2C9*3 carriers tend to have a higher AUC of siponimod compared to subjects not carrying the *3 allele. Consequently, the PK of siponimod was assessed in CYP2C9 extensive and poor metabolizers (CYP2C9*1*1 genotype and CYP2C9*2*3 or *3*3 genotypes, respectively) in [Study A2128]. In addition, two PopPK analyses on Phase I/II and Phase III data identified CYP2C9 as a significant predictor of siponimod systemic clearance.

	In clinical DDI studies, a 2-fold higher and a 2-fold lower siponimod exposure was observed when co-administered with fluconazole (a moderate CYP2C9/CYP3A4 inhibitor) and with rifampin (a moderate CYP2C9/strong CYP3A4 inducer), respectively. Complementary PBPK modeling indicated that with decreased CYP2C9 metabolic activity in the respective genotypes, a stronger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated, especially for inhibitors. Under the proposed genotype-based dosing recommendations, siponimod exposure is predicted to increase by 1.05-1.71-fold across genotypes in presence of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole), moderate CYP3A4 inhibitors (e.g. erythromycin), or weak CYP3A4/2C9 inhibitors (e.g. fluvoxamine) when compared to CYP2C9*1*1 subjects receiving a 2 mg qd maintenance dose without co-administration of any CYP2C9/CYP3A4 perpetrator drug. In presence of moderate CYP2C9 /CYP3A4 inhibitors (e.g. fluconazole), siponimod exposure is expected to be 1.78-2.15-fold higher in all genotypes except CYP2C9*2*2. A larger increase of 2.73-fold is predicted for the CYP2C9*2*2 patients. Strong CYP3A4/moderate CYP2C9 inducers (e.g., rifampin, carbamazepine) are predicted to reduce siponimod exposure by approximately 61% to 76%. Moderate CYP3A4 inducers (e.g. modafinil) are predicted to reduce siponimod exposure by approximately 19% to 51%.
Risk factors and risk groups	Patients with CYP2C9*3*3 genotype
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 included following recommendations: • Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Siponimod should not be used in patients with a CYP2C9*3*3 genotype • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes. SmPC section 4.3 includes following contraindications: Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metabolizer). SmPC Section 4.4 included following recommendations: • Before initiation of treatment with siponimod, patients should be genotyped for CYP2C9 to determine their metaboliser status. • Patients homozygous for CYP2C9*3 should not be treated with siponimod, use in these population results in substantially elevated siponimod plasma levels. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes to avoid increased exposure to siponimod. SmPC Section 4.5 included following recommendations: • Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is

	not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor.
	• Due to an expected reduction in siponimod exposure, appropriateness and possible benefit of the treatment should be considered when siponimod is combined
	  • with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype.
	  • with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype.
	Pack size:
	Pack of 120 film-coated tablets of 0.25 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (4 tablets of 0.25 mg).
	Additional risk minimization measures:
	Educational materials for HCPs and patients/care givers:
	- HCP checklist
	- Patient/Caregiver Guide

Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-8 Important potential risk: Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML), and opportunistic infections, other than cryptococcal meningitis

Evidence for linking the risk to the medicine	In the Phase 3 study, decrease in lymphocyte count observed in patients in the siponimod 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues siponimod therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase 3 PopPKPD]. There was no increase in the number of infections following siponimod treatment compared to placebo, or with increasing average siponimod steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Herpes viral infections (other than VZV re-activation) based on the risk term were reported similarly for patients in the siponimod 2 mg group [26 (2.3%)] and the placebo group [14 (2.3%)]. Cases of herpes viral infections, opportunistic infections (includes cryptococcal infections) and PML were observed while on treatment with other S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal.

Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in *case* of an MS relapse.
Risk minimization measures	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of PML and instruction for immediate reporting to physician during or after stopping the treatment with siponimod. SmPC section 4.3 includes following contraindications: Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 included following recommendations: • Before initiating treatment, a recent complete blood count should be available. • Delay the Siponimod treatment in patients with active infection until resolution. • Vigilance for infection during Siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. • Stop Siponimod treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Siponimod therapy. • Exercise caution when Siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Siponimod treatment and for 4 weeks after stopping the Siponimod treatment. • Cases of progressive multifocal leukoencephalopathy (PML) have been reported with another sphingosine 1-phosphate receptor modulator, If a patient is suspected with PML, siponimod treatment should be suspended until PML have been excluded. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers: - HCP checklist - Patient/Caregiver Guide
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-9 Important potential risk: Thromboembolic events

Evidence for linking the risk to the medicine	Current evidence is based on the clinical and post-marketing data from other S1P modulator (Fingolimod) where a causal relationship is not yet established.

Risk factors and risk groups	Elderly age and advanced disease with disability (immobility), preexisting cardiovascular disease including hypertension are risk factors for thromboembolic events. Since this is a potential risk, no attributable increase due to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 includes following recommendations: - Use of siponimod is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure. SmPC section 4.4- Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, siponimod should not be used in patients with uncontrolled hypertension during treatment initiation. SmPC section 4.8- Hypertension as an ADR **Additional risk minimization measures**: None
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-10 Important potential risk: Malignancies (excluding BCC)

Evidence for linking the risk to the medicine	Non-clinical data:
	• At therapeutic doses, siponimod has no generalized immunosuppressive properties as it neither impairs in vitro T- or B-cell activation or proliferation, cytokine or antibody production nor does it alter the capacity to mount an immune response to neo-antigens or pathogens in vivo.
	• Siponimod is non-genotoxic
	• The 2 years carcinogenicity studies in rodents identified:
	  • hemangiosarcoma in mice, with unlikely human relevance
	  • Thyroid tumors in rats, with no human relevance
	  • Lymphosarcoma in mice, with unknown human relevance

Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at increased risk for malignancies. Since this is a potential risk, no attributable increase due to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations:

	Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV- B radiation or PUVA- photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed, and also recommends to limit the exposure to sun and UV rays. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers: - HCP checklist - Patient/Caregiver Guide
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-11 Important potential risk: Reproductive toxicity

Evidence for linking the risk to the medicine	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod-induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat/F1 generation pups and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day. The safety margin is < 1-fold.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.3 contraindicates the use of siponimod during pregnancy and in women of childbearing potential not using effective contraception. SmPC Section 4.4 includes following recommendation: • 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 discontinuation SmPC Section 4.6 and PL section 2 included effective contraception recommendations. Need for negative pregnancy test prior to siponimod treatment initiation. When stopping siponimod therapy for planning a pregnancy the possible return of disease activity should be considered SmPC Section 4.6 and PL section 2 included recommendation not to breast-feed while on siponimod treatment. **Additional risk minimization measures:**

	Educational materials for HCPs and patients/care givers - HCP checklist - Patient/Caregiver Guide card - Pregnancy Reminder Card for women of childbearing potential
Additional pharmacovigilance activities	CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM).

Table 13-12 Important potential risk: Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)

Evidence for linking the risk to the medicine	Cases of PRES have been reported in the clinical trials and in the post-marketing setting of fingolimod (included as ADR in fingolimod SmPC). In the clinical studies ADEM like rare events occurred in patients treated with fingolimod at higher dose (1.25 mg or 5mg).
Risk factors and risk groups	Since this is a potential risk, no attributable increase to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 includes recommendation that physician should promptly schedule complete physical and neurological examination, and should consider magnetic resonance imaging when patient on siponimod develops any unexpected neurological symptoms/signs or accelerated neurological deterioration. PL section 2 included recommendation on monitoring of symptoms and report immediately to physician. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - HCP checklist - Patient/Caregiver Guide.
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

Table 13-13 Missing information: Safety in patients over 60 years old (including elderly)

Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 includes following recommendations: • 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. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Table 13-14 Missing information: Use during lactation

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 and PL section 2 included recommendation not to breast-feed while on siponimod treatment. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None.

Table 13-15 Missing information: Long-term safety risks

Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	CBAF312A2304 (EXPAND) Phase 3 study extension part See section II.C of this summary for an overview of post-authorisation development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of siponimod.

II.C.2. Other studies in post-authorization development plan

Table 13-16 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CBAF312A2304 (EXPAND) Phase 3 study extension part	The Extension Part will allow patients to continue treatment with open-label BAF312 and aims to provide additional long-term safety data as well as additional information on efficacy measures.
CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM)	The overall objective of the siponimod PRegnancy Outcome Intensive Monitoring program is to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before (up to 10 days before last menstrual period (LMP)) and during pregnancy
CBAF312A2006 HCP and patient/caregivers Survey	The objective of this survey, amongst HCPs and patients/caregivers in selected European countries, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behavior around specific siponimod safety measures