16 December 2021
EMA/CHMP/11848/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mayzent

International non-proprietary name: siponimod

Procedure No. EMEA/H/C/004712/X/0007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

BCS	Biopharmaceutics classification system
CFU	Colony Forming Units
EC	European Commission
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
KF	Karl Fischer titration
PA	Polyamide
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PVC	Polyvinyl chloride
QC	Quality control
RH	Relative humidity
SmPC	Summary of product characteristics
TAMC	Total aerobic microbial count
TSE	Transmissible spongiform encephalopathy
TYMC	Total combined yeasts/moulds count
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 29 April 2021 an extension of the marketing authorisation.

The MAH applied for an addition of a new strength of 1 mg film-coated tablet. The RMP is updated in accordance.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Maria del Pilar Rayon

The application was received by the EMA on	29 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 July 2021
The PRAC Rapporteur's first Assessment Report was circulated to all	09 August 2021

PRAC and CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	16 September 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	14 October 2021
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 November 2021
The PRAC Rapporteurs circulated the PRAC Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mayzent on	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory condition that causes neuro-axonal injury in the Central Nervous System (CNS) leading to permanent and severe neurological impairment and disability. The most common onset MS form (relapsing-remitting MS, RRMS) is characterised by acute episodes of neurological dysfunction named relapses followed by variable recovery and periods of clinical stability. There are different authorised disease modifying therapies (DMT) for patients with RRMS.

More than 50% of patients who suffer from a RRMS will within a median time of 15 to 20 years from onset, develop a secondary progressive multiple sclerosis (SPMS) characterized by sustained disability with or without superimposed relapses.

2.1.2. Epidemiology

MS is the most common cause of serious neurological disability in young adults. It is estimated that more than 2.3 million people are affected by MS worldwide. The prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) and lowest in sub-Saharan Africa and East Asia at 2.1 and 2.2 per 100,000, respectively. MS typically starts between 20 to 40 years of age.

Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive MS (PPMS), where there is no gender prevalence difference.

2.1.3. Aetiology and pathogenesis

While the exact cause of MS is unknown, it is assumed that MS is mediated by an autoimmune process triggered by an infection or other environmental factors, superimposed on a genetic predisposition. The major contributors to this process are macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system. From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they target myelin antigens. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and release of cytokines are the incipient cause of tissue damage in MS not only to the myelin sheath but also to the underlying axons. This process happens over time and results in repeated attacks (clinically eloquent or not). During the acute phase, demyelination and inflammation impair or interrupts nerve transmission, giving rise to clinical signs and symptoms. Relapses are considered the clinical expression of acute inflammatory focal lesions. Afterwards, remaining permanent symptoms (sequelae) are due to permanent neuro-axonal loss or permanent injured and demyelinated neurons. Elements from both adaptive (B and T cells) and innate (monocytes, natural killer cells and dendritic cells) immune systems all are involved in any stage of MS. During the RRMS phase, the accumulation of disability (disability worsening or progression) is mostly due to lack of complete recovery of focal inflammatory lesions. In the SPMP phase, accumulation of disability is explained by the conjunction of pathological mechanisms including focal inflammatory activity (particularly relevant in SPMS with relapses and acute lesions) and failure of biological compensation of the CNS damage (impaired remyelination and lack of biological redundancy).

2.1.4. Clinical presentation, diagnosis

The most commonly onset MS phenotype (85% of patients) is RRMS clinically characterized by relapses. Nearly half of the RRMS patients will develop within 20 years a SPMS clinically characterized by disability worsening. There are no clear criteria that mark the transition from RRMS to SPMS. The transition is determined retrospectively based on evidence that disability progression had occurred independently of relapses, though relapses and focal inflammatory activity may continue to be present. In fact, the SPMS is a heterogeneous population including patients with relapses (usually with a prominent development of T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) lesions) and other patients without relapses. The term "relapsing MS" (RMS) applies to those affected patients either with a RRMS or SPMS with superimposed relapses. The pathological mechanism underlying relapses and typical radiological T2-FLAIR lesions is acute focal inflammatory activity. Regardless of other potential pathological mechanisms, lack of complete recovery from focal inflammatory lesion causes accumulation of disability. Therefore, patients with relapsing MS, despite suffering from different MS forms, constitute a common target for current treatment options. Clinical manifestations in RRMS may depend on affected CNS regions. In SPMS, accumulated CNS damage is usually presented as reduced ambulation and cognitive impairment, bulbar dysfunction, visual impairment, impaired arm function, fatigue, pain and depression and sphincter control issues.

2.1.5. Management

The standard of care for acute relapses is methylprednisolone i.v. Methylprednisolone shortens the duration of a relapse but has no influence on its sequelae. Plasmapheresis may improve recovery from relapse in steroid-resistant cases, but this is rarely used. Disease-modifying therapies (DMT) aim to

modify the course of the disease by suppressing or modulating the immune responses involved in MS pathogenesis. Biologicals (therapeutic proteins, monoclonal antibodies) and small molecules have been approved for use in this therapeutic context. DMTs aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options i.e. treatment is restricted to patients with rapidly evolving multiple sclerosis or those who had a suboptimal response to prior therapies. Currently 12 DMTs are available (country/regional differences exist) for the treatment of MS (interferon beta-1a and interferon beta-1b, peginterferon beta-1a, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, alemtuzumab, ocrelizumab, cladribine, and mitoxantrone). Most are approved for RRMS or relapsing forms of MS (RMS, defined as RRMS and SPMS with relapses). Products for both RRMS and RMS were approved based on treatment effect on relapses, MRI lesion activity, and, some for the delay in disability worsening. Interferon beta (IFNB)-1b is approved in the EU for patients with SPMS with active disease as evidenced by relapses. The two trials in SPMS presented as efficacy data for marketing authorization showed a consistent 30% reduction in frequency of relapses and inconsistent results for the primary endpoint "time to confirmed progression" (31% reduction in time to disability progression in one trial and no significant delay in the other trial including patients with overall less active disease than in the other study).

2.2. About the product

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator that selectively targets S1P receptor subtypes 1 and 5. 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.

The EU Mayzent initial Marketing Authorization Application was granted in January 2020 for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Mayzent is currently authorised as a 0.25 and 2 mg film-coated tablets. The purpose of this Line Extension Application is to register the new strength of Mayzent 1 mg film-coated tablets.

The approved maintenance dose for siponimod is 1 mg or 2 mg once daily after initial dose titration depending on the patient CYP2C9 genotype. Currently, the patients with a CYP2C9*2*3 or *1*3 genotype achieve the recommended 1mg maintenance dosage by taking four tablets of 0.25 mg. The proposed 1 mg tablet is therefore being introduced as a convenience for these patients.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as film-coated tablets containing 1 mg of siponimod as active substance. The active substance contains siponimod as a fumaric acid co-crystal. This line extension application introduces a new 1 mg strength as a convenience to patients whose recommended dose is 1 mg, currently taken as four 0.25 mg tablets.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, crospovidone, glycerol dibehenate and colloidal anhydrous silica;

Tablet coating: polyvinyl alcohol, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172), talc, soya lecithin and xanthan gum.

The product is available in PA/alu/PVC/alu blisters as described in section 6.5 of the SmPC.

2.3.2. Active Substance

The proposed new 1 mg film-coated tablet is manufactured using the same active substance (siponimod fumaric acid) manufactured by the same manufacturers and process as used in the approved 0.25 and 2 mg tablets. The information presented by the applicant in the dossier was already assessed in the original submission and there have been no subsequent changes.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as violet white, round, biconvex, bevelled-edged film-coated tablets of approximately 6.1 mm diameter with company logo on one side and "L" on the other side. The tablets are distinguished from the other marketed strengths by colour (0.25 mg: pale red; 2 mg: pale yellow) and debossing. The weight of core and coated tablets is identical, irrespective of strength. The composition of the 1 mg strength is the same as for the other strengths except for the amount of lactose monohydrate, which is adjusted to account for the different amount of active substance, and the film-coating which has a different colour.

Siponimod fumaric acid is a BCS class II compound with good absorption characteristics but practically insoluble in aqueous media, although solubility increases slightly at low pH or above pH 6.8. Limits for the particle size distribution have been set in the active substance in line with phase III clinical batches and afford sufficiently stable active substance.

The development of the 1 mg strength was based on the well-established formulation and robust manufacturing process of the approved 0.25 mg and 2 mg strengths.

The excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards where appropriate. Suitable specifications have been provided for the non-pharmacopoeial film-coating pre-mixes. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.3.1 of this report.

In vitro dissolution profiling was conducted to support the use of 1 x 1 mg tablet in place of 4 x 0.25 mg tablets. The data provided demonstrates that patients can switch between 4 x 0.25 mg tablets and a single 1 mg tablet.

The QC dissolution method for 1 mg is the same as approved for 0.25 mg and 2 mg. Suitable limits have been included in the specification.

The manufacturing process of the 1 mg strength is the same as approved for 0.25 mg and 2 mg and consists of combining the active substance and excipients, tableting and film-coating steps. The development data provided is considered sufficient.

The primary packaging is PA/alu/PVC/alu blisters as for the already approved strengths of 0.25 mg and 2 mg. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: sequential blending of solid ingredients, tabletting, film-coating and packaging. The process is considered to be a non-standard manufacturing process due to the low active substance content.

Major steps of the manufacturing process have been validated on three consecutive commercial scale batches according to the process description. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The critical steps have been defined and suitable controls are applied.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, mean mass, identity, water content, dissolution, uniformity of dosage units, assay, degradation products and microbial enumeration.

Limits for impurities and degradation products have been set according to ICH Q3B and are acceptable. The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk from different potential sources was considered and deemed to be negligible. Testing of finished product batches indicated that all elemental impurities were well below the relevant thresholds and thus, no additional controls are required.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three production scale batches of the 1 mg tablets were generated according to the ICH guidelines. Samples were stored under a series of conditions and for variable durations: at either -20 °C or 40 °C/75% RH for up to 6 months; at 5 °C, 25 °C/60% RH, 30 °C/65% RH and 30 °C/75% RH for up to 24 months. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, dissolution, assay, degradation products, loss on drying and microbial enumeration. The analytical procedures used are stability indicating.

Under refrigerated conditions, no significant changes were observed for any of the measured parameters. At 25 °C, a small increase in degradation products and drop in assay was observed. The amount of degradation was greater at higher temperatures and humidities. It was deemed that a small increase in degradation and reduction in assay was acceptable to allow patients to store tablets in a more conventional fashion, i.e. at ambient temperature rather than in the refrigerator.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product was not found to be photosensitive.

Based on available stability data, the proposed shelf-life of 2 years stored not above 25 °C as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the 1 mg tablets should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

No new non-clinical data was submitted which was considered acceptable to the CHMP.

2.5. Clinical aspects

No new clinical data was submitted which was considered acceptable to the CHMP.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

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

2.6.2. Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None proposed				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None proposed				
Category 3 - Required additional pharmacovigilance activities				
CBAF312A2304 (Extension Part) Status: Ongoing	The Extension Part will allow patients to continue treatment with open-label siponimod up to 7 years and aims to provide additional long-term safety data as well as additional information on efficacy measures.	• Varicella-zoster virus (VZV) Infection reactivation • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Basal cell carcinoma (BCC)	Periodic update	Each PSUR
			Final report	30-Jun-2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		• Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis • Cryptococcal meningitis • Potential long-term safety implications in CYP2C9 poor metabolizers • Thromboembolic events • Malignancies (excluding BCC) • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses) • Long-term safety risks		
CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM)	The overall objective of the siponimod PRIM 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.	Reproductive toxicity	Periodic update	Each PSUR
			Final report	PSUR 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CBAF312A2006 Healthcare professionals and patient/caregivers survey	The objective of this survey is to measure whether healthcare professionals (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 Mayzent (siponimod) safety measures.	To measure the effectiveness of HCP educational material	Final report	31-Dec-2025

2.6.3. Risk minimisation measures

Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities

Varicella-zoster virus (VZV) infection reactivation	**Routine risk minimizations measures:**
	SmPC Section 4.8 (Undesirable effects).
	PL section 4 (possible side effects).
	SmPC section 4.3 contraindicates use of siponimod in 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.
		Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
		None
		Additional pharmacovigilance activities:
		CBAF312A2304 (EXPAND) Phase III study extension part.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• 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 - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Cryptococcal meningitis	**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 history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 includes following recommendations • Patients with symptoms and signs of CM should undergo prompt diagnostic evaluation • Stop siponimod treatment until the exclusion of the diagnosis of CM. • Appropriate treatment should be initiated, if CM is diagnosed **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: AE follow-up checklist for adverse reaction Adjudication of OIs (including CM) cases. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part.
Bradyarrhythmia (including conduction defects) during treatment initiation	**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 on reinitiation of treatment if a dose is missed during the first 6 days of treatment or when maintenance treatment is interrupted for 4 or more consecutive daily doses.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None. **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities

	SmPC section 4.3 contraindicates use of siponimod 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
	• 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 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
		CBAF312A2304 (EXPAND) Phase III study extension part.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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 initiation 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 material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Macular edema	**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,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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. • Siponimod should be discontinued if a patient develops macular edema • Siponimod therapy should not be initiated in patients with macular oedema until resolution. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Basal cell carcinoma	**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 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. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part.

Safety concern	Risk minimization measures	Pharmacovigilance activities

Potential long-term safety implications in CYP2C9 poor metabolizers	**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 the following recommendation:
	• Use of siponimod is contraindicated in 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 must 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 level.
	• 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, caution should be applied 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:
		Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
		None
		
		Additional pharmacovigilance activities:
		CBAF312A2304 (EXPAND) Phase III study extension part

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• 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). • Pack of 28 (or 98 in some countries) film-coated tablets of 1 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 (1 tablet of 1 mg). **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML), and opportunistic infections, other than cryptococcal meningitis	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of PML and CM instruction for immediate reporting to physician during or after stopping the treatment with siponimod. SmPC Section 4.3 includes following recommendations: - Siponimod is contraindicated in 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,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up checklist for adverse reaction Adjudication of opportunistic infections (including PML) cases. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part

Safety concern	Risk minimization measures	Pharmacovigilance activities
	siponimod treatment should be suspended until PML have been excluded. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	
Thromboembolic events	**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, 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 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities**: CBAF312A2304 (EXPAND) Phase III study extension part.
Malignancies (excluding BCC)	**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 material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part.
Reproductive toxicity	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates the use of siponimod during pregnancy and in women of	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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 and recommendation to have a negative pregnancy test before initiating treatment with siponimod. 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 material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide - Pregnancy reminder card for women of childbearing potential (WOCBP)	**reactions reporting and signal detection:** No. **Additional pharmacovigilance activities**: CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM)
Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)	**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. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up checklist for adverse reaction. **Additional pharmacovigilance activities**: CBAF312A2304 (EXPAND) Phase III study extension part.
Safety in patients over 60 years old (including elderly)	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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.
Use during lactation	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Long-term safety risks	**Routine risk minimization measures:** None. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase III study extension part

2.6.4. Conclusion

The CHMP considered that the risk management plan version 3.1 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the

basis of a bridging report making reference to Mayzent 0.25 mg and 2 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

The quality data are considered acceptable.

No new preclinical or clinical data have been submitted for this 1mg film-coated tablets line extension, which is acceptable.

The CHMP agreed that there is no change to the overall benefit/risk for Mayzent as detailed in the initial Marketing Authorisation of Mayzent.

3.1. Conclusions

The overall benefit/risk balance of Mayzent 1 mg film-coated tablets is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the benefit-risk balance of Mayzent 1 mg film-coated tablets is favourable in the following indication:

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Mayzent subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

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:

- <u>Potential long-term safety implications in CYP2C9 poor metabolisers:</u>
  - 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.

- <u>Bradyarrhythmia (including conduction defects) during treatment initiation:</u>
  - 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 medications, calcium channel blockers (such as verapamil, diltiazem) and other medications (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 periodically during treatment.
  - 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:
    - A case of cryptococcal meningitis (CM) has been reported for siponimod. Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent with cryptococcal meningitis; appropriate treatment, if diagnosed, should be initiated. Siponimod treatment should be suspended until CM has been excluded.
    - Cases of progressive multifocal leukoencephalopathy (PML) have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment should be suspended until PML has been excluded.

- <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.
    - 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. 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.
- The signs and symptoms of infection during, and up to one month after treatment with siponimod need to be reported immediately to the prescriber.
- 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 regularly in some cases while on treatment with siponimod and should be cautioned against exposure to sunlight without protection. Also, these 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.
- 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.