NOVARTIS

Mayzent® (siponimod)

# Survey among healthcare professionals and MS patients/caregivers in selected European countries to evaluate the knowledge required for the safe use of Mayzent

## REDACTED PROTOCOL

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## RMP information

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|---|---|
| **Title** | Survey among healthcare professionals (neurologists treating patients with MS along with MS specialist nurses) and patients in selected European countries to evaluate the knowledge required for the safe use of Mayzent (siponimod) |
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| **Marketing Authorization Holder(s)** | Novartis Europharm Limited<br>Vista Building<br>Elm Park<br>Merrion Road<br>Dublin 4<br>Ireland |
| **Joint PASS** | No |
| **Research questions and objectives** | The objective of this survey is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge of specific Mayzent (siponimod) safety measures. |
| **Countries of survey** | Germany, Italy, France, Netherlands, Nordics (Denmark, Finland, Norway, Sweden) and Poland |
| **Author** | [redacted] |

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List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| CNS | Central nervous system |
| CM | Cryptococcal meningitis |
| CV | Cardiovascular |
| ECG | Electrocardiogram |
| EDSS | Expanded Disability Status Scale |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EMA | European Medicines Agency |
| GDPR | General Data Protection Regulation |
| HCPs | Healthcare professionals including neurologists treating patients with MS and MS specialist nurses |
| MAH | Marketing Authorization Holder |
| MS | Multiple Sclerosis |
| PML | Progressive multifocal leukoencephalopathy |
| RMS | Relapsing MS |
| RRMS | Relapsing Remitting MS |
| RMP | Risk Management Plan |
| SPMS | Secondary Progressive MS |
| VZV | Varicella-zoster virus |

# 1 Responsible parties

The execution of this protocol is the responsibility of the following parties:

- Main Protocol Author
  [redacted], United Kingdom [redacted]
- Marketing Authorization Holder (MAH)
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  Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland
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- MAH representative
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## 1.1 Marketing Authorization Holder

The MAH contact facilitates Competent Authority Submissions.

## 1.2 MAH representative

The MAH representative for this survey will be overseeing a contract organization delegated to serve as survey coordinating center. The contract organization, [redacted] is responsible for the operational conduct of the survey including recruiting of the participating HCPs (neurologists treating patients with MS and MS specialist nurses) and patients/caregivers throughout the duration of the survey, facilitating data collection and ensuring adherence to local regulations including data privacy. In addition, the contract organization, [redacted] will draft the study documents, perform analysis and produce planned interim and final study reports.

# 2 Abstract

**Title**

Survey among healthcare professionals (neurologists treating patients with MS and MS specialist nurses) and MS patients/caregivers in selected European countries to evaluate the knowledge required for the safe use of Mayzent (siponimod).

**Rationale and background**

In order to increase understanding of the effective and safe use of Mayzent (siponimod) HCPs and patients/caregivers will be provided educational information on the specific areas of interest as agreed with EMA in the Mayzent EU RMP v2.1, dated 29-Oct-2020.

As per guidelines on GVP Module XVI rev 02 dated Mar 2017, evaluating the effectiveness of additional risk minimization measures proposed in the RMP is necessary to establish whether an intervention has been effective or not, and if not, why and which corrective actions are necessary.

This survey is a required additional pharmacovigilance activity that is included in the Mayzent EU RMP v2.1.

**Survey objectives**

The objective of this survey, amongst HCPs and patients/caregivers in selected European countries (including Germany, Italy, France, Netherlands, Nordics and Poland), is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge of specific Mayzent (siponimod) safety measures.

Primarily the educational materials content focus on developing an understanding of the need for CYP2C9 genotyping prior to treatment initiation, managing bradyarrhythmias on treatment initiation, including the receipt and proper usage of the titration starter pack and educating both HCP and patients on need for treatment adherence. They also describe the management of infections, macular edema, skin malignancies and pregnancy considerations.

**Study design**

Survey to be completed independently by HCPs (neurologists treating patients with MS and MS specialist nurses) and patients/caregivers.

The web-based survey will be conducted in EU countries where Mayzent (siponimod) is available on the market and reimbursed for at least 6 months, to capture the knowledge and understanding of specific Mayzent safety measures by HCPs and patients/caregivers with access to Mayzent (siponimod).

**Population**

The study will be conducted across two populations:

1. HCPs who prescribe, monitor and oversee the management / or provide in person medical supervision of patients on Mayzent (siponimod). These will include treating physicians as well as MS specialist nurses across identified EU markets that represent distribution and prevalence of MS and countries that will be included in the launch program over time (including Germany, France, Italy, Netherlands, Nordics and Poland)

2. Patients/Caregivers of patients who are taking Mayzent (siponimod) to treat their MS and according to the prescription of their neurologists across EU markets that will be included in the launch program (including Germany, France, Italy, Netherlands, Nordics and Poland)

**Survey components**

The HCP surveys will comprise of:

A) Screening section for eligibility and demographic profiling information such as years in practice, clinical setting and patient caseload.

B) Main questionnaire for eligible participants collecting data relating to the education materials provided for initiation, maintenance and treatment interruption of Mayzent (siponimod) directed at healthcare professionals

The patient/caregiver surveys will comprise of:

C) Screening section for eligibility and demographic profiling information such as diagnosis with MS, age, time since diagnosis of MS and level of engagement with the disease

D) Main questionnaire for eligible participants collecting data relating to the education materials provided for initiation, maintenance and treatment interruption for Mayzent (siponimod) directed at patients and caregivers

To limit the occurrence of missing data, the survey will be designed to capture a "Do not know" response if the respondent cannot answer a question and the survey will be programmed to prompt respondents to answer a given question prior to being able to move to a subsequent question.

**Data source**

Data sources will include:

- For HCPs: eligibility materials administered through recruitment screener document, self-administered online survey questionnaire
- For Patients/caregivers: eligibility materials administered through the recruitment screener document, self-administered online survey questionnaire

**Study size**

A total sample of N=200 completed surveys from HCPs (140 neurologists treating patients with MS and 60 MS specialist nurses) and N=110 completed surveys from patients/caregivers will take part from Germany, France, Italy, Netherlands, Nordics (Denmark, Finland, Norway, Sweden) and Poland.

1. The sample size is determined based on a number of criteria:
    a. Ability to reflect a representative view across the physician treating patients with ~~SP~~MS
    b. Feasibility of survey completion within the 4 month timeframe after contacting the respondent)

c. Acceptable statistical confidence to support intended analysis (minimum level for any analytic variable to not be below N=35)

**Data Analysis**

The analysis will be descriptive in nature. For continuous variables, counts, means (with standard deviations), medians and ranges will be provided. For categorical variables, frequencies and percentages (with 95% confidence intervals) will be provided. Missing data will be noted for each variable.

**Expected results**

After a planning phase, where the questionnaire will be developed and piloted, the survey will be conducted in participating countries at a fixed period post launch.

The pilot will compromise of 3-5 surveys to be completed during an initial phase. The data from the pilot phase will be sense checked to ensure the survey is working appropriately, and the respondents will be asked whether they easily understood the questions.

The survey results will inform the impact that educational materials have on the knowledge of physicians in the adoption of the risk minimization interventions required for the use of Mayzent (siponimod). Actions from the analysis of the results will either confirm that the education materials in the form disseminated have effectively communicated the appropriate treatment approach or identify areas where additional information or clarifications need to be addressed. We will ideally want to achieve correct response, responses that match the information provided in the education materials, among at least 70% of all respondents.

# 3 Amendments and updates

None currently

# 4 Milestones

**Table 4-1 Planned dates of key milestones**

| Milestone | Planned Date |
|---|---|
| Protocol submission to EMA | 31-Mar-2020 |
| Start of Study in the first country | 31 Oct 2021 |
| Interim analysis (IA) of the study | 31 Dec 2022 |
| IA report submitted to EMA | 31 Jul 2023 |
| End of data collection in last country | 30 Sept 2024 |
| Final report of study results submitted to EMA | 31 Sept 2025 |

Data collection to be carried out not before 6 months post-Mayzent (siponimod) launch in respective markets, with a breakdown of expected product launch and study fielding dates included in Table 5-2. An extended timeline is given to allow for the eventualities of delayed fieldwork as a result of delayed product launch or reimbursement, or where additional fieldwork is required to implement and measure corrective actions (e.g. second round of recruitment to get the minimum number of questionnaires needed to do the analysis). Nevertheless, in order to deliver results in a shorter time an interim analysis (IA) will be conducted by the end of 2022 (December), when the survey is expected to be finalized in most of the countries (six out of the nine countries included in the study) and the sample size could exceed 100 surveys for HCPs and 40 surveys for patients/caregivers (sufficient for acceptable statistical confidence).

**Table 4-2 Planned dates of Mayzent (siponimod) launch**

| Milestone | Planned Product Launch Date | Planned Study Start Date |
|---|---|---|
| Germany | Feb-2020 | Oct 2021 |
| Sweden | Aug-2020 | Oct 2021 |
| Denmark | Feb-2021 | Oct 2021 |
| Finland | Jul-2021 | Feb 2022 |
| Netherland | Jan-2021 | Oct 2021 |
| Poland | May-2021 | Dec-2021 |
| Italy | May-2021 | Dec-2021 |
| France | Q4-2022 | Jul-2023 |
| Norway | Jun-2021 | Jan-2022 |

# 5 Rationale and Background

## 5.1 Background

Multiple sclerosis (MS) is the most common autoimmune demyelinating disorder of the central nervous system (CNS), affecting more than 2.3 million individuals worldwide (Multiple Sclerosis International Federation 2021). Approximately 85% of patients present with a relapsing-remitting course with neurological stability between relapses (RRMS). With time, an increasing number of these patients (>50% within 15 to 20 years) evolve to the secondary progressive phase (SPMS) of the disease in which there is a decreasing frequency (or absence) of relapses and in parallel a steady accumulation of disability (Lublin and Reingold, 1996), (Lublin et al 2014). Patients who have transitioned to the SPMS stage of disease are particularly characterized by reduced ambulation, such that aids for walking are needed and eventually wheelchairs are required to get about. In addition, these patients experience cognitive impairment, bulbar dysfunction, visual impairment, impaired arm function, fatigue, pain and depression, coupled with often severe sphincter control issues. All of which leads to a markedly reduced quality of life as well as reduced employment opportunities, frequently with a major impact on other family members.

There is a clear unmet need for an effective and safe therapy for SPMS. No approved MS DMT has demonstrated efficacy in reducing disability progression in patients with typical SPMS to date.

Mayzent (siponimod) is the first disease-modifying therapy that has demonstrated efficacy on reducing the risk of disability progression in a Phase 3 trial in typical SPMS patients across the ambulatory spectrum of SPMS, including many who had reached a non-relapsing stage and a high level of disability (Kappos L et al 2018). The effect of siponimod on disability progression demonstrated in this trial is clinically relevant. In an advanced patient population, and in the high EDSS range studied (EDSS 3-6.5), where over 50% of patients enrolled needed walking aids (EDSS score of 6.0 or higher), changes in EDSS are clinically meaningful as they are mostly irreversible and affect relevantly day to day activities.

The consistent and clinically relevant effects in reducing the risk of disability progression in an advanced ambulatory SPMS population addresses the unmet need of those patients. Extensive subgroup analyses (pre-defined and post-hoc) support consistent treatment effects (Kappos L et al 2018).

In addition to its effects on disability progression, Mayzent (siponimod) treatment reduced brain volume loss, an objective marker linked to disability progression in SPMS. Strong anti-inflammatory effects (relapse reduction, reduction of inflammation on MRI) address additionally clinical needs of SPMS patients with relapses (Kappos et al 2018).

The overall safety profile of Mayzent (siponimod) is consistent with the known safety profile of fingolimod, another S1P receptor modulator (Kappos et al 2018). In total, 1784 MS patients received Mayzent (siponimod) at doses ranging from 0.25–10 mg once daily in the clinical development program. Of these, over 1737 MS patients were treated with at least one dose of siponimod 2 mg, the proposed dose for registration, or higher. The cumulative exposure of clinical trial MS patients to Mayzent (siponimod) is over 4500 patient-years.

As noted with fingolimod, increased rates of liver function test abnormalities, macular edema, hypertension, and bronchoconstriction AEs were observed compared to placebo. In most cases differences between Mayzent (siponimod) and placebo were small and reversible upon discontinuation of treatment. The severity of most events was mild or moderate and the events were either transient, preventable or can be readily managed.

Apart from varicella-zoster virus reactivation, which, although incidences were low, was reported more frequently on Mayzent (siponimod) compared to placebo, infectious complications do not appear on current evidence to be significantly increased. There was no imbalance in the frequencies of malignancies, although the number of events to date, and the duration of follow-up, is relatively limited and does not permit conclusions at this time on any potential long-term risk.

Dose titration successfully mitigated heart rate and AV conduction effects upon Mayzent (siponimod) treatment initiation and treatment initiation was well tolerated. This supports treatment initiation of Mayzent (siponimod) without a need for post-dose observation in patients with normal cardiac status. Patients with underlying cardiac disease (including AV conduction delays), despite the benign nature of the observed events, may require additional observation on treatment initiation to determine individual cardiovascular response to Mayzent (siponimod) therapy. As the most relevant changes are dynamic decreases in heart rate, which were most marked on Day 1, post-dose observation for a limited time period on Day 1 is recommended in patients with underlying cardiac disease.

Due to the potential for teratogenicity, Mayzent (siponimod) should not be used during pregnancy unless benefit to the patient is deemed to exceed the potential risk to the fetus. Women of childbearing potential should be counseled as to the potential risk to the fetus and advised to use effective contraception while on Mayzent (siponimod) and for at least 10 days following discontinuation of drug. Likewise, breast-feeding should not be performed in MS patients receiving Mayzent (siponimod) therapy due to the risk of adverse reactions in the nursing infant as a result of Mayzent (siponimod) in breast milk (SmPC of siponimod).

### Recommended use and RMP summary (Mayzent EPAR product information and BAF312 EU RMP v 2.1)

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 RMP details important risks of siponimod, how these risks can be minimized, and how more information will be obtained about siponimod's risks and uncertainties (missing information).

Important, identified or potential, risks of siponimod are outlined below:

- Identified important risks:
    - Varicella-zoster virus (VZV) Infection reactivation
    - Cryptococcal meningitis

  - Bradyarrhythmia (including conduction defects) during treatment initiation
  - Macular edema
  - Basal cell carcinoma
- Potential important 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
  - Reproductive toxicity
  - Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)

These risks need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. As part of these activities the MAH has develop and deliver educational material to HCPs (a checklist) and patients/caregiver (a Guide), to help them to better knowledge how siponimod should be used. The area of interest covered by these materials are outlined below, along with a brief description of the action to follow:

1. Treatment with siponimod should be initiated and supervised by a physician experienced in the management of multiple sclerosis.
2. CYP2C9 poor metabolizers. Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status (see sections 4.4, 4.5 and 5.2).

   In patients with a CYP2C9*3*3 genotype, siponimod should not be used (see sections 4.3, 4.4 and 5.2).

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

   The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg.
3. Mayzent is taken once daily.
4. Bradyarrhythmia. Treatment has to be started with a titration pack that lasts for 5 days. Treatment starts with 0.25 mg once daily on days 1 and 2, followed by once-daily doses of 0.5 mg on day 3, 0.75 mg on day 4, and 1.25 mg on day 5, to reach the patient's prescribed maintenance dose of siponimod starting on day 6.

   During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food.
5. VZV reactivation and other serious infections. Prior to siponimod treatment initiation:

• Test for 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.

• Cases of 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.

6. Macular edema. 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 edema. 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.

7. Reproductive toxicity. 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.

8. Unexpected neurological or psychiatric symptoms or signs. 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.

9. Perform skin examination and be vigilant for skin malignancies

## 5.2 Rationale

As part of the Mayzent EU RMP v2.1, dated 29-Oct-2020, that was agreed with EMA, Novartis have developed an MEA that includes a survey of HCPs and patients/caregivers who receive educational materials provided as part of the Mayzent (siponimod) RMP.

The educational materials are aimed at providing HCPs and patients/caregivers with information on the risk minimization interventions required for the safe usage of Mayzent (siponimod).

These address the following areas of interest:

- Bradyarrhythmia (including conduction defects) during treatment initiation
- Infections, including varicella zoster reactivation, reactivation of the other viral infections, PML and other rare opportunistic infections including cryptococcal meningitis
- Reproductive toxicity
- Macular edema
- Potential long-term safety implications in CYP2C9 poor metabolizers (on siponimod exposure and effects of CYP2C9/3A4 inhibitors and inducers)
- Malignancies including skin malignancies
- Unexpected neurological or psychiatric symptoms/signs (e.g.; PRES, ADEM, Atypical MS Relapses)

Novartis will conduct the survey not before 6 months post Mayzent (siponimod) reimbursement with HCPs and patients/caregivers to evaluate the impact of the proposed risk minimization measures. The survey will establish whether HCPs and patients/caregivers have received the education materials, and that they demonstrate accurate understanding of what is required when administering Mayzent (siponimod).

# 6 Research Objectives

The objective of this survey, amongst HCPs and patients/caregivers in selected European countries, is to evaluate whether the HCP and patient/ caregivers educational materials are clearly presented, and convey knowledge that support the effective use of Mayzent's (siponimod) at initiation and throughout treatment. Assessing, firstly, the dissemination of the education material, and upon receipt of the materials assess prescribing physicians' knowledge and understanding relating to the appropriate initiation as per detailed in the educational information provided, measured according to the percentage (%) of correct responses given across the sample, where 70% achieving the correct answer is deemed as acceptable, and the distribution of incorrect answers will be evaluated to assess the extent of deviation and potential mitigation required. The educational material particularly focuses on the following important initiation processes: CYP2C9 genotyping prior to treatment initiation, monitoring of

bradyarrhythmias on treatment initiation, treatment initiation recommendations and usage of titration starter pack, and information on treatment adherence. In addition, education materials will also inform on procedures for the management of infections, macular edema, skin malignancies and pregnancy considerations.

# 7 Research Methods

## 7.1 Study design

This is a multinational, questionnaire-based, cross-sectional survey to be conducted among 1) healthcare professionals and 2) patients/caregivers.

## 7.2 Healthcare provider approach and recruitment

HCPs include both neurologists treating patients with MS and MS specialist nurses.

**Neurologists treating patients with MS and MS specialist nurses recruitment process**

The survey will assess the HCPs knowledge in relation to the initiation and continued management of their role in prescribing Mayzent (siponimod) for their SPMS patients.

A web-based survey approach will be used in all selected countries. Recruitment to establish eligibility for participation will take place not before 6 months following the reimbursement of Mayzent (siponimod) in each market.

HCPs will be recruited via established healthcare professional panels that are maintained for market research purposes through a third-party recruitment provider. Healthcare professionals in the panel have opted in for market research, and all members are validated at registration to confirm their identity. A briefing document, designed to confirm eligibility based on specific profile information (for example specialty type, HCP grade), will be provided to the panel provider. Members from the panel will be confirmed as eligible through completion of this step. If a list exists of targeted Healthcare professionals from Novartis, a list match will be carried out to supplement panel-based healthcare professionals.

HCPs who are deemed eligible through this recruitment stage will be sent an email to introduce the study and provide a link to the online survey. The Healthcare professional will be asked to provide informed consent at the start of the online survey and answer screening questions to confirm their eligibility to participate. If they qualify, they can then initiate the main survey. HCPs eligible will be sent up to three reminders after initial contact to remind them to complete the survey. All HCPs meeting the inclusion criteria will be invited to complete the safety questionnaire – there will be no additional selection criteria applied.

Participating HCPs will be requested to complete the questionnaire within two weeks of enrollment in the survey.

The intention is to implement the survey at different times depending on the country but at a fixed period after the launch (i.e. month 6/7, a minimum of 6 months) in all countries.

The survey will be conducted in EU countries where Mayzent (siponimod) is available on the market and reimbursed for at least 6 months.

Since Mayzent's (siponimod) launch will be staggered, the survey will be conducted at the same time point from launch in each country, rather than waiting for the last country to gain approval. This reduces the chance of any bias introduced by some HCPs having longer or shorter durations of experience with the Mayzent (siponimod).

Each estimate by country reflects the universe of expected eligible HCPs and patients/ caregivers for recruitment into the study. Explanation for this estimation is detailed below the Table 8-1.

A total sample of N=200 HCPs (140 neurologists and 60 MS nurses) and 110 patients will take part from Germany, France, Italy, Netherlands, Nordics (Denmark, Finland, Norway, Sweden) and Poland.

- Markets within the sample have been selected according to Mayzent (siponimod) launch plans and MS prevalence
- The markets are representative of countries across the European Union.
  - Representation across north and south regions
  - Representation across east and west regions

**Table 7-1 Sample estimate by country**

| | **Physicians / subset of MS nurses** | **Patients/caregivers** |
|---|---|---|
| Germany (North/West) | N=55 | N=25 |
| France (North/West) | N=45 | N=25 |
| Italy (South/West) | N=35 | N=20 |
| Netherlands (North/West) | N=20 | N=10 |
| Nordics (Denmark, Finland, Norway Sweden) (North/West) | N=20 | N=15 |
| Poland (South/East) | N=25 | N=15 |
| Total | 200<br>(140 neurologists and 60 MS nurses) | 110 |

We recommend the target sample of N=200 based on a number of criteria:

a. Feasibility of contact and survey completion within the 4 month timeframe in each country

b. Ability to reflect a representative view across the physicians who are treating patients with MS and specifically SPMS patients

c. Provision of acceptable statistical confidence to support intended analysis (minimum level for any analytic variable to not be below N=35); [Note: we provide descriptive analysis for the region (European level) with potential analysis between north and south European countries, and do not provide country by country analysis.]

   i. In a circumstance where recruitment does not yield the full proposed sample, analysis will be undertaken on a smaller sample where acceptable statistical confidences is achieved.

In order to achieve the recommended sample of 200 completed questionnaires, we have assumed a response rate approximately 12% (1 out of 8) based on previous experience in this therapy area, and therefore expect to contact ~ 1700 physicians / specialist nurses.

**Physician eligibility criteria**

In order to be eligible to enroll and complete the survey, the physician must have experience in treating RMS patients.

The physician must have also personally prescribed Mayzent (siponimod) within 3 months prior to the date of the survey. The level of experience of prescribing and thus their experience of managing patients on Mayzent (siponimod) will be assessed for each participating physician during the screening process.

- Physicians will be considered eligible for the survey if they meet the following screening criteria:
  - Care for relapsing MS (RMS) patients
  - Personally prescribed disease modifying therapies to MS patients, and;
  - Have prescribed Mayzent (siponimod) in at least 1 SPMS patient.

**Nurse eligibility criteria**

In order to be eligible to enroll and complete the survey, the MS specialist nurse must have experience in providing supportive care for RMS patients.

The MS specialist nurse must have also have personally managed a patient that has been prescribed Mayzent (siponimod) within 3 months prior to the date of the survey. The level of experience to manage patients on Mayzent (siponimod) will be assessed for each participating nurse during the screening process.

- Nurses will be considered eligible for the survey if they:
  - Provide supportive care for RMS patients
  - Have initiated and/or managed the use of Mayzent (siponimod) in at least 1 SPMS patient.

## 7.3 Patient approach and recruitment

The survey will assess the patient's knowledge in relation to their usage of Mayzent (siponimod) treatment.

A web-based survey approach will be used in each of the countries, however a paper survey can be made available to patient/caregiver if requested due to limited online access and capabilities. The paper-based survey will be identical to the online survey and will also be self-reporting. All answers from the paper-based survey will be entered into the online survey by the MAH representative so that all the data is held in one place.

Patients / caregivers will be recruited in multiple ways.

1. **HCP referrals**

HCPs that have been contacted and found to be eligible for the study will also be asked to refer all patients that they have prescribed Mayzent (siponimod) for inclusion in the study. HCPs will then send an invitation letter to all potentially eligible patients / caregivers. The invitation letter will be pre-drafted by the MAH and MAH representative and will contain the rationale for the research, overview of length and type of survey and contact details. Interested patients /caregivers respond to the invitation letter and are then screened for eligibility, if the criteria are met, they are asked to provide consent to participate in the study and are sent the online study link or provided with the paper survey either in person or via post.

2. **Direct patient recruitment**

To supplement HCP referral, patients/caregivers will also be recruited via patient panels, patient associations, and recruiter databases. All communications will be pre-drafted by the MAH and the MAH representative and initial communications will include information about the rationale and the format of the study, as well, broadly outlining the type of people the study are looking to include. Any interested patient is then asked to contact the recruiter (representative from the in-market agency) for further details around the length and type of survey and asked a number of eligibility questions via the telephone.

**Patient (caregiver of patient meeting this profile) eligibility criteria**

Patient inclusion / exclusion criteria include:

- Have been initiated onto Mayzent (siponimod) to treat their MS since reimbursement

If the eligibility criteria are met, the patients will be asked to provide consent to participate in the study and will be sent the online study link or provided the paper version of the survey in person or via post.

A total sample of N=110 patients will take part. The distribution across markets will be targeted as follows:

**Table 7-2 Patient/caregiver sample by country**

| | Patients/caregivers |
|---|---|
| Germany | N=25 |
| France | N=25 |

| | |
|---|---|
| Italy | N=20 |
| Netherlands | N=10 |
| Nordics (Denmark, Finland, Norway, Sweden) | N=15 |
| Poland | N=15 |
| Total | 110 |

The target sample of N=110 based on a number of criteria:

a. Feasibility of contact and survey completion within a reasonable time period (4 months)
    i. A smaller sample of n=110 MS patients/ caregivers is proposed due to reduced accessibility and feasibility of survey completion within this population and within the 4 month timeframe to complete this assessment and analyse results to determine that all education materials are providing the support required for the proper administration of Mayzent, or any areas requiring mitigation are identified.

b. Ability to reflect a representative view across the patient population who would be targeted for treatment with Mayzent (siponimod)

c. Accountability for using a physician referral approach and requiring patient opt in through this channel - whilst each physician will be required to have one SPMS patient initiated on Mayzent we will experience physicians who may not be willing or able to refer, or we will experience referrals of patients who choose not to opt in. With regards to the latter scenario it is to the patients' discretion that they contact the recruitment partner to opt in to participate. Thus, the rationale for the smaller patient sample when compared to the HCP sample.

d. Provision of acceptable statistical confidence to support intended analysis (minimum level for any analytic variable to not be below N=35); Note we provide descriptive analysis for the European region and do not expect country by country analysis
    i. In a circumstance where recruitment does not yield the full proposed sample, and where additional strategies to improve recruitment (i.e. extension of the data collection period in the study countries which fall short of the required sample proportions, increased recruitment efforts to contact additional HCPs/patients/caregivers, or engagement of additional recruitment partners) have already been implemented, analysis will be undertaken on a smaller sample where acceptable statistical confidences is achieved.

## 7.4 Variables

Structure of the surveys

The HCP / patient surveys will comprise of two parts:

1. Eligibility criteria check

2. For eligible subjects, the main safety survey

## 7.5 HCP eligibility check

The eligibility will be established using a screening document designed to include all relevant qualification criteria, which are answered and entered into a database via a survey link. All data captured on the online server to be downloaded at the end of fieldwork.

The screening document will take a structured approach to capture physician/ specialist nurse eligibility, including demographics, working environment and caseload.

**Table 7-3 Overview of HCP screening questions**

| Section | Content |
|---|---|
| Section 1 | Survey introduction |
| Section 2 | Demographics and screening questions<br>• Specialty<br>• Grade<br>• Practice type<br>• Hospital type<br>• Number of patients per year you treat/provide supportive care<br>• RMS patient workload (# patients seen in last 3 months)<br>• SPMS patient workload (# patients seen in last 3 months)<br>• Number of patients with SPMS prescribed Mayzent (siponimod) |

*Content included, but not limited to the items included in the table

## 7.6 HCP safety questionnaire

A structured questionnaire will be used for this survey.

The survey will be aimed at characterizing the participating HCP and evaluating their knowledge relative to the risk minimization interventions required for the safe use of Mayzent (siponimod). Given the same safety materials will be used to educate physicians and nurses, the same survey will be utilised in assessment of both of these HCP groups. Language and content is deemed suitable for both groups, given eligibility criteria requires respondents to have experience in treatment of MS.

The questionnaire will address the following aspects:

- Confirmation of receipt of materials
- Physician's / nurses awareness and understanding of Mayzent (siponimod) educational materials

- Physician's/nurses understanding of how Mayzent (siponimod) should be used in clinical practice

**Table 7-4 Overview of HCP main survey questions to assess effectiveness of educational materials in HCP survey**

| Section | Content |
|---|---|
| Section 1 | Objectives: To assess the dissemination of the education material, and upon receipt of the materials assess prescribing physicians' knowledge and understanding relating to the appropriate initiation as per detailed in the educational information provided<br>• To assess: if materials are being received Identification of appropriate patients for prescribing<br>• Initiation steps<br>• Treatment dosing schedule |
| Section 2 | Objectives: To assess HCP knowledge and understanding of specific safety measures when treating patients with Mayzent (siponimod)<br>To assess steps when treating patients with sinus bradycardia, 1st/2nd degree AV block or history of myocardial infarction or health failure<br>• Patient types not recommended for prescribing<br>• Monitoring<br>• Additional management and observation requirements |
| Section 3 | Objectives: To assess knowledge of procedures for the management of infections, macular edema, skin malignancies and pregnancy considerations.<br>To assess steps in ophthalmology checklist, managing infection risk, pregnancy, liver function and skin examinations<br>• Requirements for need of ophthalmologic examination<br>• Requirements for need of skin examination<br>• Counselling on when to report signs and symptoms<br>• Vaccination history<br>• Steps when serious infection is experienced<br>• Contraception and pregnancy<br>• Managing unexpected neurological and/or psychiatric symptoms |

*content included, but not limited to items in table

## 7.7 Patient / caregiver eligibility check

Screening data reflecting confirmed eligibility will be captured by the recruiter via the telephone assisted recruitment approach and then entered into the online survey by the recruiter. All data captured on the online server to be downloaded at the end of fieldwork.

The screening document will take a structured approach to capture patient/ caregiver eligibility.

- Prescribed Mayzent for the treatment of MS
- Demographics; time since diagnosis with MS, age, employment status, engagement with disease

**Table 7-5 Overview of Patient / Caregiver screening questions**

| Section | Content |
|---|---|
| Section 1 | Survey introduction |
| Section 2 | Demographics and screening questions<br>• Patient / Caregiver identification (*no personal data)<br>• Diagnosis history<br>• Treatment (current and historic)<br>• Age<br>• Gender<br>• Employment status |

*Content included, but not limited to the items included in the table

## 7.8 Patient / caregiver safety questionnaire

A structured questionnaire will be used for this survey.

- Confirmation of receipt of materials
- Awareness and understanding of Mayzent (siponimod) educational materials (knowledge aspects)
- Assess how Mayzent (siponimod) is used by the patient

**Table 7-6 Overview of Patient/Caregiver main survey questions to assess effectiveness of educational materials in patient/caregiver survey**

| Section | Content |
|---|---|
| Section 1 | Objectives: To assess the dissemination of the education material, and upon receipt of the materials assess patient/caregivers' knowledge and understanding relating to the appropriate initiation as per detailed in the educational information provided<br>To assess:<br>• If materials are being received<br>• Knowledge of testing before initiation<br>• Knowledge at treatment initiation |
| Section 2 | Objectives: To assess patient/caregivers' knowledge and understanding of specific safety measures when being treated with Mayzent (siponimod)<br>To assess understanding of side effects and potential risks<br>• Macular Oedema<br>• Infection<br>• Impaired liver function<br>• Pregnancy requirements<br>• Missed doses<br>• Skin malignancies |

*content included, but not limited to items in table

## 7.9 Translation of survey eligibility screening document and questionnaire

The questionnaire will be translated into the native languages of the participating countries. Accuracy of the translation will be ensured by independent proof-reading of all translations followed by a final review and approval of the translations by the local Novartis affiliate in each of the participating countries.

## 7.10 Data sources

Data sources will include:

- For Healthcare professionals: eligibility materials administered through recruitment screener document, self-administered online survey questionnaire
- For Patients: eligibility materials administered through recruitment screener document, self-administered online survey questionnaire

Both the HCP and the patient online surveys (or paper where required) will take approximately 15 minutes to complete. All data entered into the survey will be collected as self-administered online survey or entered into the database once submitted in paper format.

## 7.11 Statistical analysis and sample size

The proposed survey analysis is descriptive in nature. Results will measure the number of HCPs and patients/caregivers that correctly answer questions. Questions will only cover the information in these materials, and nothing extraneous to treatment use.

For continuous variables, counts, means (with standard deviations), medians and ranges will be provided. For categorical variables, frequencies and percentages (with 95% confidence intervals) will be provided.

In order to address the primary outcome of the study we have calculated the sample size considering a 70% of correct answers among HCPs and patients/caregivers. See tables below.

**Table 7-7 Precision estimates - HCPs**

| Sample Size | % Correctly answered questions in the questionnaire per HCP | Lower Limit | Upper Limit | 95% CI |
|---|---|---|---|---|
| 200 | 90 | 85.85 | 94.15 | 4.15 |
| 200 | 80 | 74.46 | 85.54 | 5.54 |
| 200 | 70 | 63.65 | 76.35 | 6.35 |
| 200 | 60 | 53.22 | 66.78 | 6.78 |

**Table 7-8 Precision estimates – Patient/caregivers**

| Sample Size | % Correctly answered questions in the questionnaire per patient | Lower Limit | Upper Limit | 95% CI |
|---|---|---|---|---|
| 110 | 90 | 84.40 | 95.60 | 5.60 |
| 110 | 80 | 72.53 | 87.47 | 7.47 |
| 110 | 70 | 61.45 | 78.55 | 8.55 |
| 110 | 60 | 50.85 | 69.15 | 9.15 |

As a result, a total sample number of 310 (200 HCPs and 110 patients/caregivers) completed questionnaires will be targeted across the countries indicated.

With expected launch dates for Mayzent (siponimod) in the markets in scope spread over an extended period, an interim analysis will be conducted at the point that the majority of markets are completed, and with a minimum sample of 100 HCPs and 40 patients/caregivers.

## 7.12 Expected results

The survey results will measure whether the HCP and patient/caregivers educational materials convey knowledge that support the effective use of Mayzent's (siponimod) at initiation and

during early use. Actions from the analysis of the results will either confirm that the education materials in the form disseminated have effectively communicated the appropriate treatment approach, or identify areas where additional information or clarifications need to be addressed.

## 7.13 Study limitations

A key requirement of this study is that it reflects a representative view across the physician, nurse and patient/caregiver population in the context of those that have used or been involved in the treatment and management of Mayzent (siponimod). To minimize sample bias, HCPs will be recruited via databases and patient/caregivers will be recruited primarily via physician referral, reflecting their real caseload, or through patient databases. The use of databases for HCPs or patients may in itself introduce an unavoidable element of bias due to participants being predisposed to market research. However this is minimized by inviting a random sample from the database, rather the targeting specific individuals. There may be a requirement to use patient associations to supplement patient/caregiver recruitment and in this instance steps will be taken to ensure the sample is not skewed too heavily towards patients more engaged with their disease. For both HCPs and patients/caregivers profiling questions within the screener will be used to ensure the sample is representative of the population.

A sub-set of MS specialist nurses involved in the education and management of Mayzent (siponimod) patients will be included in the HCP sample. A 30% of the final HCP sample quota will be applied to ensure MS nurses are not overrepresented.

There is a requirement for a paper-based tool to be available as an alternative to the online data collection tool. MS patients with secondary progressive disease may have some limitations, such as dexterity problems. As a consequence, there is a need to accommodate those patients finding it too difficult to access or complete online surveys by providing an alternative paper-based approach. Having two data collection mediums could introduce bias, but this is mitigated by all questions still being self-reported (without interviewer assistance). Furthermore, the paper questionnaire questions will be laid out exactly as the online questionnaire, with no differences to wording. Steps will be taken to ensure access to the online platform is as straightforward as possible to limit the number of completes via the paper survey.

Results from the paper-based survey will be manually inputted into the online survey so all data is captured within the same software. To minimize data errors, the data inputted will undergo a quality control process, involving a second individual checking the data and a number of logic checks embedded in the survey to flag any potential issues. The patient/career would have consented to be contacted by the MAH representative in the event any of the information provided on the paper-based survey is missing, incomplete or eligible.

There may be some recall bias associated with HCPs and patient / caregivers thinking back over time when answering the survey. To minimize this bias we ask respondents to answer questions about patients they have seen in the last 6 months.

Another potential limitation is that respondents have to access the survey in their own time and hence the response rate could be low. In order to mitigate this possibility, the healthcare professional will be contacted through email multiple times (three). IDs will be associated with HCPs and patients/caregivers provided with the link / paper copy of the questionnaire. For the online respondents, we can track whether the link has been activated and whether the survey

has been completed or is only partially completed as a given time. Follow up contacts to encourage completion will be limited so as not to inconvenience the respondent.

Descriptive analysis will be provided for the region (European level). Country by country analysis will not be provided as the sample size within some individual countries is not sufficient to support statistical confidence (minimum level for any analytic variable to not be below N=35). Therefore we will be unable to assess if the educational materials work similarly across countries, but expect to provide some insight into the effectiveness of the materials at a sub-regional (North vs. South) level.

## 7.14 Data management and quality control

Participant answers to the online survey will be collected using Confirmit horizons software and the data exported via SPSS (.save) and analyzed using Q-research software.

The data is stored in London, England. The data is isolated on the server.

The Confirmit Horizons SaaS (software as a service) hosting environments are not "cloud" based. Horizons SaaS hosting environments store the data physically in a specific data center, and the management of the data center is hosted by Rackspace. Rackspace holds the following security specifications, including ISO27001, Payment Card Industry (PCI DSS), ISO 9001, and is SOC 11 audited in accordance with SSAE16/ ISAE 3402.

In order to comply with the General Data Protection Regulation (GDPR) only a minimum amount of personal data will be collected in order to fulfill the purposes of the survey. This data will be retained only for as long as the duration of the project.

On Confirmit Horizons SaaS there is a 'countdown' feature whereby the project owner defines a retention period for the whole survey database. The data will be deleted from the Confirmit Horizons SaaS environment at that date. Prior to the deletion date, the system will send an email reminding the project owner that the data will be deleted in X days

To ensure the validity of the results, it is necessary to ensure that the data collected are of good quality. This implies minimizing any missing data and ensuring the data collected is accurate.

- Materials will be designed to contain clear respondent instructions at each question.
- The survey will primarily consist of questions that include a list of predefined answers for participants to select from when making their responses.
    - Pre-defined answer list to be randomized where relevant to ensure responses are not led and so provide an accurate reflection of respondent knowledge
- Logic checks will be programmed in the internet script to define expected ranges/answers, based on existing therapeutic knowledge, as well as "live" checks and error messages to prompt the patient to check missing data and illogical answers whilst they are completing the survey.
- Each survey will be piloted by n=1 HCP and n=1 patient/caregiver, respectively, per country in advance of main fieldwork to check the design and language used in the survey is understandable and that all survey logic is implemented prior to launch.

- Each survey will be soft-launched, fielding with 10% of the sample before full launch of fieldwork. This will check that the design of the questionnaire works in practice.

# 8 Protection of Human Subjects

The online survey will include text to comply with European and individual country current legislation and industry guidelines regarding Adverse Events and informed consent. Respondents rights to privacy and protection of their personal data will be respected and identifying information such as a respondent's name, email address, home address or phone number will not be recorded.

The industry guidelines and legislation will be:

- European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Promotion of Prescription-Only Medicines to, and interactions with, Healthcare professionals 2014
- EU data Protection Directive 11995
- Regulation EU 2016/679
- EU directive on Privacy and Electronic Communications (2002/58/EC) 2003
- EFPIA Code on Disclosure of Transfers of Value from the Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations 2014

After the respondent consent has been signed, a unique link with password will be sent out to the respondents for them to complete the survey. This will ensure that respondents' identities are validated.

There will be no audio or video recording at any point of the study procedures. While we are focused on assessing understanding and knowledge, if an Adverse Event is reported then we will follow standard protocol and consent will be obtained to follow-up for contact details after informing the respondent about the purpose of the data collection and processing of personal data.

# 9 Management and reporting of adverse events

The study is not designed to collect information on individual adverse drug reactions (ADR) associated with the use of Mayzent (siponimod) or any other Novartis product. Furthermore, the majority of questions have set-choices of answers that are not designed to assess the safety or adverse events of a drug. However, there are some questions where respondents can type in their own responses and hence it is possible that during the survey, respondents may spontaneously provide information that meets the criteria for ADR. Once the total sample completes, an MAH representative will analyze the free text responses and if the MAH representative becomes aware of any adverse drug reactions regarding any Novartis product, it will be reported to the Novartis PV department within one business day of the MAH representative becoming aware of such data by:

- Completing the PV reporting form

And sending it to the local Novartis PV department within 1 business day

All events will be managed and reported in compliances with all applicable regulations and all personnel working on the study will be trained to report adverse events.

# 10 Ethical issues

As the study is capturing knowledge and not outcomes, there is no requirement to seek ethical approval.

# 11 Plans for communication of study results

Detailed written report including; methodology, survey results with statistical analysis and confidence intervals, key discussion point and conclusions. The report will be descriptive in nature and look at overall results, indicating any relevant profile or demographic differences where relevant and statistically meaningful. Recommended actions will be included based on accuracy of understanding of the factors assessed. This report will be submitted to EMA as part of a RMP commitment.

# 12 References – available upon request

Kappos L, Bar-Or A, Cree BAC, et al. (2018) Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. p. 1263-1273

Lublin FD and Reingold SC (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. p. 907-11

Lublin FD, Reingold SC, Cohen JA (2014) Defining the clinical course of multiple sclerosis (The 2013 revision). Neurology. p. 278-286

Multiple Sclerosis International Federation (2021) What is MS. MS International Federation. www.msif.org/about-ms/what-is-ms/

# 13 Appendix – Detailed survey questions

**Table A1 Questions to assess effectiveness of educational materials in HCP survey**

| Category of assessment | Question text [Answer options+] | Criteria for 'effective assessment' |
|---|---|---|
| To assess if materials are being received | Have you received the healthcare professional's checklist which outlines the considerations before, during and after treatment with Mayzent (siponimod)?<br>1. Yes<br>2. No | Majority of HCPs selecting Code 1 |
| | Have you received patient reminder cards for Mayzent (siponimod)<br>1. Yes<br>2. No | Majority of HCPs selecting Code 1 |
| To assess identification of appropriate patients for prescribing | Prior to commencing treatment with siponimod, the CYP2C9 genotype of every patient should be determined<br>Select one.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of HCPs selecting Code 1 |
| | Which of the following maintenance doses is correct for the initiation of siponimod for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?<br>Select one.<br>1. 1 mg<br>2. 1.25 mg<br>3. 2 mg<br>4. 10 mg<br>5. Don't know/ not sure | Majority of HCPs selecting code 1 |
| To assess Initiation steps | Which of the following recent (i.e., within the last six months) test results should be made available prior to treatment initiation? (Multiple response)<br>1. Transaminase and bilirubin levels<br>2. Full blood count<br>3. Cholesterol<br>4. Calcium<br>5. Glucose<br>6. None of these<br>7. Don't know/ not sure | Majority of HCPs selecting Code 1 and 2 |

| | | |
|---|---|---|
| | You have to conduct baseline electrocardiogram (ECG) in patients with sinus bradycardia (heart rate <55 bpm), first or second degree AV block or a history of myocardial infarction or heart failure.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of HCPs selecting codes 1 |
| | When, if at all, should skin examination be performed for patients treated with siponimod?<br>1. Prior to treatment initiation<br>2. Every 6-12 months following initiation<br>3. Not at all<br>4. Don't know/ not sure | Majority of HCPs selecting codes 1 and 2 |
| | For which of the following medications/therapies is co-administration not recommended?<br>1. Class Ia and III anti-arrhythmics<br>2. Anti-neoplastics<br>3. Immunosuppressive or immunomodulatory agents<br>4. Phototherapy with UV-B radiation of PUVA photochemotherapy<br>5. All of the above<br>6. Don't Know/ Not Sure | Majority of HCPs selecting code 1 and 4 |
| | Caution should be taken when switching from other disease modifying therapies due to the risk of additive immune system effects?<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of HCPs selecting code 1 |
| | Within what time period do you need to check liver transaminases before commencing patients on siponimod?<br>Please select one below<br>1. 2 months<br>2. 3 months<br>3. 6 months<br>4. 12 months<br>5. Don't Know/Not Sure | Majority of HCPs selecting code 3 |
| To assess treatment dosing schedule | An up-titration scheme is required for siponimod. Please indicate the number of days this scheme takes to complete.<br>Select one. | Majority of HCPs |

| | | |
|---|---|---|
| | 1. 3<br>2. 5<br>3. 6<br>4. 7<br>5. Don't know/ not sure | selecting code 2 |
| | When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?<br>Write in day<br>1. Don't know/ not sure | Majority of HCPs write in DAY 4 |
| | The recommended maintenance dose/s after up-titration schedule is/are:<br>Select all that might apply in any patients<br>1 0.5 mg<br>2 1 mg<br>3 1.25 mg<br>4 2 mg<br>5 Don't know/ not sure | Majority of HCPs selecting code 2 and 4 |
| | What steps need to be taken if a dose is missed for more than one day during the first 6 days of the treatment initiation? Tick all that apply<br>1. The titration schedule needs to be restarted with a new titration pack<br>2. The titration schedule needs to be re-started only if this is within the first 4 days of treatment<br>3. None, the titration is to be continued with the missing dose taken the next day<br>4. The patient shall not be further treated with siponimod | Majority of HCPs selecting code 1 |
| | Have you counselled your patients on the importance of taking their daily dose of siponimod, during both titration and maintenance phases of treatment?<br>Select one.<br>1. Yes<br>2. No | Majority of HCPs selecting code 1 |

| | | |
|---|---|---|
| To assess steps when treating patients with sinus bradycardia, 1st/2nd degree AV block or history of myocardial infarction or health failure | For which type/s of patients is Mayzent (siponimod) not recommended?<br>Please select all that apply<br>1. Patients with concomitant treatment with class Ia or class III anti-arrhythmic medications<br>2. Patients with QTC prolongation >500 msec<br>3. Patients with history of recurrent syncope<br>4. Patients with history of symptomatic bradycardia<br>5. Patients with uncontrolled hypertension<br>6. Patients with severe untreated sleep apnoea<br>7. Patients with active malignancies<br>8. Patients with controlled hypertension<br>9. Patients treated with benzodiazepines<br>10. Patients treated with beta-blockers<br>11. None of these<br>12. Don't know/ not sure | Majority of HCPs selecting codes 1-7 |
| | How many hours should a patient with sinus bradycardia, 1st/2nd degree AV block or history of myocardial infarction or health heart failure be monitored at treatment initiation?<br>Select one.<br>1. 3<br>2. 5<br>3. 6<br>4. 8<br>5. Don't know/ not sure | Majority of HCPs selecting code 3 |
| | What finding on the ECG at the end of the 6-hour monitoring period would warrant initiation of additional appropriate management and until resolution continued observation?<br>Please select all that apply<br>1. New onset second degree or higher AV block<br>2. QTc>500 msec<br>3. Hypotension<br>4. Transient sinus bradycardia of 50 bpm<br>5. None of these<br>6. Don't know/ not sure | Majority of HCPs selecting codes 1 & 2 |
| | Does your center perform the first dose monitoring (FDM) for patients with cardiovascular (CV) risk or do you send your patients to other specialized MS centers for FDM? | Majority of HCPs selecting codes 1 & 2 |

| | | |
|---|---|---|
| | Select one that best applies<br>1. Perform first dose monitoring in my own center<br>2. Send patients to other specialized centers for first dose monitoring<br>3. Do not conduct first dose monitoring in patients with CV risk | |
| To assess steps in ophthalmology checklist, managing infection risk, pregnancy, liver function and skin examinations | For which patients due to be initiated on siponimod should you conduct an ophthalmologic examination before starting treatment?<br>1. Diabetes mellitus<br>2. Uveitis<br>3. History of retinal disorders<br>4. Severe myopia<br>5. None of these<br>6. Don't know / not sure | Majority of HCPs selecting codes 1 & 2 |
| | At what time after starting treatment should a full ophthalmologic evaluation be performed?<br>1. 1-2 months<br>2. 3-4 months<br>3. 5-12 months<br>4. 13-24 months<br>5. Don't know/ not sure | Majority of HCPs selecting code 2 |
| | Patients should be counselled to report signs and symptoms of infection immediately to their prescriber.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of HCPs selecting code 1 |
| | Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection<br>Select one.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of HCPs selecting code 1 |
| | You should check varicella zoster virus antibody status in patients without a healthcare professionally confirmed history of chicken pox.<br>Select one.<br>1. Yes | Majority of HCPs selecting code 1 |

| | | |
|---|---|---|
| | 2. No<br>3. Don't know/ not sure | |
| | Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?<br>1. 2 weeks<br>2. 1 month<br>3. 2 months<br>4. 3 months<br>5. Don't know/ not sure | Majority of HCPs selecting code 2 |
| | What action should be taken if a patient reports serious infection during treatment on siponimod?<br>Please select all that apply or "Both of the above"<br>1. Perform prompt diagnostic evaluation and initiate appropriate treatment if diagnosed<br>2. Consider treatment suspension if there are signs and symptoms that may be suggestive of progressive leukoencephalopathy (PML) or cryptococcal meningitis (CM)<br>3. Both of the above<br>4. Don't Know/ Not Sure | Majority of HCPs selecting code 3 |
| | After stopping treatment, for how long does siponimod remain in the blood?<br>1 5 day<br>2 10 days<br>3 15 days<br>4 20 days<br>5 Don't know/ not sure | Majority of HCPs selecting code 2 |
| | For how long should a female patient use effective contraception following discontinuation of siponimod, for at least [INSERT]?<br>Write in a time period in days<br>1. Don't know/ not sure | Majority of HCPs writing in 10 DAYS |
| | For patients who become pregnant during treatment, what is the correct approach from the options below.<br>Select all that apply<br>1. Patient treatment should be discontinued immediately<br>2. Patient should be titrated off treatment | Majority of HCPs selecting codes 1 & 3 |

| | | |
|---|---|---|
| | 3. Pregnancy should be reported to Novartis<br>4. None of these<br>5. Don't know/ not sure | |
| | What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia?<br>1. Continue as nothing serious could happen<br>2. Check liver enzymes<br>3. Discontinue treatment if significant liver injury is confirmed<br>4. Don't know/ not sure | Majority of HCPs selecting codes 2 & 3 |
| + - Order of pre-defined answer lists will be displayed in random order unless there is a logical sequence that would result in randomization creating confusion for the respondent. | | |

**Table A2 Questions to assess effectiveness of educational material in patients/caregivers survey**

| Category of assessment | Question text [Answer options+] | Criteria for 'effective assessment' |
|---|---|---|
| To assess if materials are being received | Have you / the person you are caring for with MS received any education materials for Mayzent (Siponimod)?<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of patients selecting Code 1 |
| To assess knowledge of testing before initiation | For what reasons will the doctor do a test before you get ready for treatment with Mayzent (siponimod) (Please select all that apply)<br>1. CYP2C9 genotype (a gene that can modify how fast or slow siponimod can be metabolized – or transformed - within your body)<br>2. White blood cell count<br>3. Liver function<br>4. Hepatitis Type B<br>5. Hematocrit (concentration of red cells in your blood)<br>6. None of these<br>7. Don't know/ not sure | Majority of patients/ caregivers selecting Code 1, 2 & 3 |

| | | |
|---|---|---|
| | If you need to be vaccinated for chicken pox, for how long after the full course of vaccination must you wait to start your treatment with Mayzent (siponimod)<br>1. 6 months<br>2. 4 months<br>3. 2 months<br>4. 1 month<br>5. Don't know/ not sure | Majority of patients/ caregivers selecting code 3 |
| | For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with Mayzent (siponimod)? (Please select all that apply)<br>1. Have or have had previously visual disturbances or vision problems in the center of the eye<br>2. Have or have had previously inflammation of the eye<br>3. Have or have had high blood sugar levels/Diabetes<br>4. Cataract (when the lens of your eye becomes opaque or loses its transparency)<br>5. Hypertension status<br>6. None of these<br>7. Don't know/ not sure | Majority of patients/ caregivers selecting code 1, 2 & 3 |
| | If you have an underlying heart problem or are taking medication that can cause the heart rate to slow down, the doctor will do a test called an electrocardiogram (ECG) to check the rhythm of your heart before starting treatment with Mayzent (siponimod). Select one.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of patients/ caregivers selecting code 1 |
| | When, if at all, may your doctor want to conduct a skin examination? (please select all that apply)<br>1. Prior to starting treatment with siponimod<br>2. Every 6-12 months when receiving treatment with siponimod<br>3. Not at all<br>4. Don't know/ not sure | Majority of patients/ caregivers selecting code 1 and 2 |

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| To assess knowledge at treatment initiation | At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask you to the stay in the clinic after taking the first dose so that your blood pressure and pulse can be monitored?<br>1. 3 hours<br>2. 6 hours<br>3. 9 hours<br>4. Not applicable, I don't have heart problems<br>5. Don't know/ not sure | Majority of patients/caregivers selecting code 2 |
| | At the time when you first started Mayzent (siponimod): For what reason may you need to spend an extended period of time being monitored within a clinic?<br>1. You experience a feeling of anxiety<br>2. Your ECG (electrocardiogram – to check the rhythm of your heart) shows abnormalities<br>3. Your blood pressure goes up<br>4. Your blood sugar levels increase<br>5. None of these<br>6. Don't know/ not sure | Majority of patients/caregivers selecting code 2 |
| | Are you aware that there is a period of titration / up-dosing at the start of treatment with Mayzent (siponimod).<br>Select one.<br>1. Yes<br>2. No | Majority of patients/caregivers selecting code 1 |
| | For how many days is the titration / up-dosing schedule (pack)?<br>1. 3 days<br>2. 5 days<br>3. 6 days<br>4. 7 days<br>5. Don't know/ not sure | Majority of patients/caregivers selecting code 2 |

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| | If you miss a tablet on one day during the first 6 days of the treatment, you will need to get a new titration pack and start the treatment again on day 1.<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of patients/caregivers selecting code 1 |
| To assess understanding of side effects and potential risks | What are the symptoms that may mean you are experiencing macular oedema (accumulation of water on the central part of your retina, an inner layer of your eye that is responsible for having clear central vision)? (Please indicate all that apply)<br>1. Blurred or wavy vision<br>2. Changes in color / color looking faded<br>3. Loss of vision<br>4. Redness in the eye<br>5. Eye pain<br>6. None of these<br>7. Don't know/ not sure | Majority of patients/caregivers selecting codes 1, 2 & 3 |
| | What are the symptoms that may mean you are experiencing an infection including brain infection?<br>1. Fever<br>2. Flu-like symptoms<br>3. Headache with or without stiff neck<br>4. Nausea and or confusion<br>5. Swelling of the extremities due to accumulation of water<br>6. None of these<br>7. Don't know/ not sure | Majority of patients/caregivers selecting codes 1 - 4 |

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| | What are the symptoms that may mean you may be experiencing impaired liver function? Select all that apply<br>1. Unexplained nausea<br>2. Vomiting<br>3. Abdominal/Stomach pain<br>4. Fatigue (overall felling of tiredness or lack of energy)<br>5. Rash (a change in the color or in the texture of your skin that can cause itchiness)<br>6. Yellowing of the eyes or the skin<br>7. Dark urine<br>8. Headache<br>9. Fever<br>10. Productive cough<br>11. Blurred vision<br>12. Joint pain<br>13. None of these<br>14. Don't know/ not sure | Majority of patients/caregivers selecting codes 1 - 7 |
| | Which skin conditions, if any, should be reported immediately to your doctor?<br>1. Skin nodules (e.g. shiny or pearly patches)<br>2. Patches or open sores that do not heal within a few weeks<br>3. Dryness<br>4. None of these<br>5. Don't know/ not sure | Majority of patients/ caregivers selecting code 1 and 2 |
| | You should avoid exposure to sunlight without protection while on Mayzent (siponimod)<br>1. Yes<br>2. No<br>3. Don't know/ not sure | Majority of patients/caregivers selecting code 1 |
| | *Female patients of childbearing age only:* You must avoid getting pregnant while on Mayzent (siponimod).<br>4. Yes<br>5. No<br>6. Don't know/ not sure | Majority of patients/caregivers selecting code 1 |

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| | *Female patients of childbrearing age only:* For how many days after stopping treatment with Mayzent (siponimod) should you arrange reliable methods of birth control with consultation from your doctor?<br>1. 6 days<br>2. 10 days<br>3. 12 days<br>4. Don't know/ not sure | Majority of patients/caregivers selecting code 2 |
| | If you miss taking medication after you have finished your up-dosing period and you are taking your prescribed dose of maintenance, for how many days can your treatment be interrupted before you need to contact your doctor and reinitiate treatment with a new starter pack?<br>1. 3 consecutive days<br>2. 4 consecutive days<br>3. One full week<br>4. Don't know/ Not sure | Majority of patients/caregivers selecting code 2 |
| + - Order of pre-defined answer lists will be displayed in random order unless there is a logical sequence that would result in randomization creating confusion for the respondent. | | |