NOVARTIS

Global Medical Affairs (Neuroscience)

Mayzent (siponimod)

Redacted Protocol

Study No. CBAF312A2006

Non-Interventional Study Report

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

Author	PPD Novartis Healthcare Ltd

Document Status	Final
Date of final version of the study report	24-Oct-2025
EU PAS register number	EUPAS44782

PASS information

Title	Survey among healthcare professionals (neurologists treating patients with MS and MS specialist nurses) and MS patients/caregivers in selected European countries plus Canada to evaluate the knowledge required for the safe use of Mayzent (siponimod)
Version identifier of the final study report	1.0
Date of last version of the interim study report	12-Jul-2023
EU PAS register number	EUPAS44782
NIS Type	NIS with Primary Data Collection
Active substance	Siponimod
Medicinal product	Mayzent
Product reference	EMEA/H/C/004712
Procedure number	EMEA/H/C/004712/MEA/004.3
Marketing authorization holder	Novartis Europharm Limited
Joint PASS	No
Research question 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.
Country(-ies) of study	Germany, Netherlands, Croatia, Spain, Denmark, Sweden and Canada

Main author

PPD

Novartis Healthcare Ltd

Marketing authorization holder

Marketing authorization holder(s)

Novartis Europharm Limited

Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland

MAH contact person

PPD

Novartis Pharma AG, Lichtstrasse 35, CH-4002 Basel, Switzerland

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1 Abstract

Title

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

Version and date

1.0 24-Oct-2025

NIS Type

NIS with Primary Data Collection

Name and affiliation of main author

PPD

Keywords

Mayzent, Healthcare Professionals (HCPs), patients/caregivers, educational materials, multiple sclerosis, survey

Rationale and background

To enhance understanding of the effective and safe use of Mayzent (siponimod), HCPs and patients/caregivers are 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 03 dated Jul 2024, evaluating the effectiveness of additional risk minimization measures proposed in the RMP is necessary to establish whether an intervention has been effective, and if not, why and which corrective actions are necessary.

This survey is a required additional pharmacovigilance activity that is included in the current Mayzent EU RMP v7.2. and includes Canada as an additional participating country at the request of the Canadian Health Authority.

Research question and objectives

The objective of this survey amongst HCPs and patients/caregivers in selected European countries, plus Canada, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to evaluate whether the HCP and patients/caregiver educational materials are clearly presented and convey knowledge that support the effective use of Mayzent (siponimod) at initiation and throughout treatment.

The effectiveness of the educational materials was assessed using pre-specified criteria. The following criteria were applied:

- Effective receipt of educational materials: Receipt was considered effective if at least 70% of respondents reported receiving the educational materials.
- Effectiveness in increasing understanding: Each individual question was considered satisfactorily addressed if at least 70% of respondents answered the question correctly.

Primarily, the educational materials' content focuses 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 oedema, skin malignancies and pregnancy considerations.

Study design

The study included two distinct questionnaires designed to assess 1) HCPs (neurologists treating patients with MS and MS specialist nurses) knowledge in relation to their role in counselling and on-going management of patients who are receiving Mayzent treatment and 2) knowledge of patients who are receiving Mayzent or their caregivers in relation to their treatment.

Survey questions for HCPs and patients/caregivers were included to cover the important, identified or potential, risks of Mayzent.

Each questionnaire included an initial set of screening questions to confirm eligibility. Following this the HCP questionnaire comprised a total of 30 questions (two focused on receipt of educational materials resulting in 28 questions evaluating knowledge). The patient/caregiver questionnaire included a total of 19 questions (one focused on receipt of educational materials resulting in 18 questions evaluating knowledge).

Subjects and Setting

The study was 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 included treating physicians as well as MS specialist nurses
2. Patients/Caregivers of patients who are taking Mayzent (siponimod) to treat their MS and according to the prescription of their neurologists

The survey was administered in six European markets that represent distribution and prevalence of MS and where Mayzent (siponimod) was available and reimbursed for at least six months (Germany, Netherlands, Spain, Croatia, Sweden and Denmark), and Canada.

Study size

A total sample of N=220 completed surveys from HCPs (161 neurologists treating patients with MS and 59 MS specialist nurses) and N=118 completed surveys from patients/caregivers were evaluated.

Variables and data sources

Data sources included:

- 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

Statistical methods

The analysis is descriptive in nature. For continuous variables, counts, means (with standard deviations), medians and ranges are provided. For categorical variables, frequencies and percentages (with 95% confidence intervals) are provided.

Results

HCPs were asked about receipt of two specific educational materials: the prescriber's checklist and the patient reminder card. HCPs in Netherlands were not asked about the patient reminder card as this is not in use in this market. A total of 85% (n=186/220) of HCPs recall receiving the prescriber's checklist and 75% (n=146/195) had received the patient reminder cards.

A total of 56% of patients/caregivers recalled receiving educational materials for Mayzent, with 16% unsure.

Comparisons have been made between HCPs or patients/caregivers who recall receiving the educational materials and those who do not, to evaluate the impact of the educational materials on knowledge. Those who recall receiving the materials show significantly higher levels of knowledge across some topics, highlighting the positive impact of educational materials on HCP and patient/caregiver understanding of key information relating to treatment with Mayzent.

The proportion of correct responses from HCPs and patient/caregivers across the remaining questions included in the surveys shows the level of knowledge required for the use of Mayzent. Among HCPs, 75% (21/28) of the survey questions had 50% or more correct responses. This included 12/28 questions that had 70% or more correct responses and these were all questions that required a single correct response. Furthermore, 7/28 questions demonstrated a strong level of knowledge, with 90% or more of HCPs responding correctly. Topics HCPs demonstrated good knowledge of include the need to determine CYP2C9 genotype, requirement for an ECG prior to initiation, risk of additive immune effects, timeframe to check liver transaminases, need to counsel patients on taking daily dose, first dose monitoring, counsel patients to report signs of infection, caution against sunlight, need to check VZV antibody status and the timeframe to delay treatment following VZV vaccination, actions needed if a patient has a serious infection, and the correct approach if a patient becomes pregnant.

There were 9/28 questions with 50–69% correct responses (4 with multiple correct responses, and 5 with a single correct response). There were also 7/28 questions with less than 50% correct responses (4 with multiple correct responses and 3 with a single correct response). Topics where knowledge was below 50% include the correct maintenance dose for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3, appropriate timing for skin examinations, specific details of the titration schedule, knowledge of all patient types where Mayzent is not recommended, patients requiring an ophthalmologic examination, and the length of time Mayzent remains in the blood following treatment discontinuation.

Of the 8 questions for HCPs with multiple correct responses that failed to reach the 70% threshold for success, 6 of these had one or more separate correct responses that were selected by 70% or more, indicating HCPs have good knowledge of these topics but failed to meet the criteria for success defined as selecting all correct responses.

In the patient/caregiver survey, 7/18 questions had 70% or more correct responses (3 with multiple correct responses (where selecting one of these was considered correct) and 4 with a single correct response), with only one question achieving 90% or higher. Topics patients/caregivers showed good knowledge of include the need to avoid pregnancy (>90%), need for an ECG prior to initiation, need for dose titration, symptoms of infection or liver impairment, skin conditions to report to their doctor, and the need to avoid exposure to sunlight.

5/18 questions had 50–69% correct responses (1 with multiple correct responses, and 4 with a single correct response). There were 6/18 questions with less than 50% correct responses (3 with multiple correct responses, and 3 with a single correct response). Topics where knowledge was below 50% include blood tests required prior to initiation, need for eye examinations, reasons for extended monitoring at first dose, timing of skin examination, duration of titration, and number of days can skip maintenance dose.

Of the 5 questions for patients/caregivers with multiple correct responses that failed to reach the 70% threshold for success, none of these had any separate correct responses that were selected by 70% of more.

Discussion

It should be noted that overall success has been measured based on clinically meaningful results, and not always by the strictest criteria, i.e. taking the proportion of respondents who selected all correct responses and no incorrect responses, or selecting an exact response which is aligned with the educational materials. The proportion of HCPs and patients/caregivers selecting some but not all the correct responses, or selecting a clinically more conservative response, is often higher, indicating good knowledge based on clinical experience and judgement. There were 8 questions for HCPs and 7 questions for patients/caregivers that had multiple correct responses – these represent a more robust

test of knowledge than a single response question and are more difficult for HCPs or patients/caregivers to be classified as fully correct due to the need to select all the correct responses.

HCPs demonstrated appropriate knowledge for most of the important identified or potential risks of Mayzent; however, areas where HCP knowledge appeared to be incomplete with regard to key topics included the following:

- Knowledge of the recommended maintenance dosing for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3 (H-Q4)
- Understanding of all patient types where Mayzent is not recommended (H-Q16). This question had 8 correct responses, and knowledge of these was varied with 4 correct responses selected by 50% or fewer HCPs and the other 4 selected by more than 65%
- Awareness of patient types where ophthalmologic examination is required prior to initiation (H-Q20). This question had 3 correct responses, of which each were selected by between 50% and 60% of HCPs; however, less than 50% selected all three correct responses
- Length of time female patients need to use effective contraception following discontinuation of Mayzent treatment (H-Q28). The correct answer of 10 days was selected by 40% of respondents; 57% chose 10 days or more while 39% responded that they did not know/were not sure of the correct answer.

Some areas where patients/caregivers show low levels of knowledge relate to patient eligibility and steps prior to initiation, where risk of low awareness among patients/caregivers is mitigated by the involvement of an HCP, who will be responsible for ensuring appropriate tests and checks are performed prior to initiation.

Areas where there are low levels of knowledge among patients/caregivers regarding key risks included the following:

- Awareness of all symptoms of macular oedema (P-Q12)
- Awareness of all symptoms of brain infection (P-Q13)
- Awareness of all symptoms of impaired liver function (P-Q14)
- Number of days they can interrupt Mayzent treatment before they need to reinitiate treatment with an up-titration schedule (P-Q19)
- Awareness of the number of days after stopping Mayzent that effective birth control is required (P-Q18)

Patients/caregivers have awareness of some symptoms to report and, based on the criteria of selecting at least one correct response, these questions achieve the 70% threshold for success. However, the proportion of patients/caregivers with awareness of all symptoms is low.

Although knowledge in some areas did not meet the designated threshold, it was unclear if the respondents were completing the survey from recall/memory or were using the educational materials while responding. The necessary information is available to HCPs and patients/caregivers in the label and patient information pack insert, in addition to being clearly explained in the educational materials. This is supported by the evidence that knowledge is higher among HCPs and patients/caregivers who recall receiving the educational materials, which demonstrates that the materials are effective at communicating the important safety information for Mayzent.

Conclusion

The survey results confirm that an acceptable number of HCPs involved in the prescribing and management of patients receiving Mayzent recall receiving the educational materials (Prescribers checklist). A lower proportion of patients/caregivers recall receiving the educational materials from their prescribers.

Patients/caregivers who were in receipt of the educational materials were more informed on some topics than those who did not recall receiving the materials, indicating that the materials were effective at communicating key messages. It is the responsibility of HCPs to distribute the materials to their patients. Ensuring that patients/caregivers receive the materials will have a positive impact on knowledge levels.

In summary, this robust assessment demonstrated overall appropriate understanding of the use of Mayzent, especially by HCPs. Several study limitations were acknowledged in relation to sampling considerations, response rate, survey question design, and reference to the educational materials.

The necessary information is available to HCPs and patients/caregivers in the label and patient information pack insert, in addition to being clearly explained in the educational materials. The educational materials have been thoroughly reviewed and are considered adequate to support the safe and effective use of Mayzent. With the completion of this study, the RMP commitment is fulfilled.

Marketing Authorization Holder(s)

Novartis Europharm Limited

Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland

2 List of abbreviations

ADEM	Acute Disseminated Encephalomyelitis.
ADR	Adverse drug reaction
BCC	Basal cell carcinoma
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
PRES	Posterior Reversible Encephalopathy Syndrome
RMS	Relapsing MS
RRMS	Relapsing Remitting MS
RMP	Risk Management Plan
SPMS	Secondary Progressive MS
VZV	Varicella-zoster virus

3 Investigators

Not applicable

4 Other responsible parties

- Main Report Authors

  PPD

  Novartis Healthcare Ltd, Hyderabad 500081, Telangana, India

- Marketing Authorization Holder (MAH)

  Novartis Europharm Limited

  Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland

- MAH contact person

  PPD Novartis Pharma AG, Lichtstrasse 35, CH-4002 Basel, Switzerland

- MAH representative

  PPD Novartis Healthcare Ltd, Hyderabad 500081, Telangana, India

The MAH representative for this survey was overseeing a contract organization delegated to serve as survey coordinating center. The contract organization, CCI 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, CCI has drafted the study documents, performed analysis and produced this study report.

5 Milestones

Table 5-1 Study milestones

	Milestones	
	Planned dates	Actual date
Start of data collection	31-Oct-2021	02-Dec-2021
End of data collection (Last date of data collection)	30-Sep-2024	16-May-2025
Registration in the EU PAS register	21-Dec-2021	21-Dec-2021
Interim Analysis	31-Jul-2023	12-Jul-2023
Final Study Report	30-Sep-2025	24-Oct-2025

6 Rationale and background

To enhance understanding of the effective and safe use of Mayzent (siponimod), HCPs and patients/caregivers are 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 03 dated Jul 2024, evaluating the effectiveness of additional risk minimization measures proposed in the RMP is necessary to establish whether an intervention has been effective, and if not, why and which corrective actions are necessary.

This survey is a required additional pharmacovigilance activity that is included in the current Mayzent EU RMP v7.2 and includes Canada as an additional participating country at the request of the Canadian Health Authority.

7 Research question and objectives

The objective of this survey, amongst HCPs and patients/caregivers in selected European countries, plus Canada, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to evaluate whether the HCP and patients/caregiver educational materials are clearly presented and convey knowledge that support the effective use of Mayzent (siponimod) at initiation and throughout treatment.

The effectiveness of the educational materials was assessed using pre-specified criteria. The following criteria were applied:

- Effective receipt of educational materials: Receipt was considered effective if at least 70% of respondents reported receiving the educational materials.
- Effectiveness in increasing understanding: Each individual question was considered satisfactorily addressed if at least 70% of respondents answered the question correctly.

Primarily the educational materials' content focuses 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 oedema, skin malignancies and pregnancy considerations. As per the protocol, the survey was designed to address the following key messages:

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.

   In patients with a CYP2C9*3*3 genotype, siponimod should not be used.

   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).

   The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg.
3. Mayzent is taken once daily. Patients should be informed about the importance of treatment adherence and instructed on what to do in the event of a missed dose.
4. Bradyarrhythmia. Treatment has to be started with a titration pack that lasts for five 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.

Special attention should be paid to steps when treating patients with sinus bradycardia, first or second-degree AV block, or history of myocardial infarction or heart failure.

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 six 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 three to four weeks after treatment discontinuation.

   • Stop siponimod treatment if patient develops 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 four 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.

   • Review vaccination history and ensure it is up to date.

   • Liver function should be assessed as per standard clinical practice and monitored during treatment as appropriate. Patients should be advised about the potential risks associated with impaired liver function.

6. Macular edema. An ophthalmic evaluation after three - four months of treatment initiation with siponimod.

   • siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema. It is recommended that these patients undergo ophthalmic evaluation prior to the initiation and during the treatment with siponimod treatment.

   • As cases of macular oedema 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 oedema. A decision on whether or not siponimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

   • 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. Contraception and pregnancy status should be regularly reviewed during treatment.

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

8 Amendments and updates to the protocol

9 Research methods

A multi-national questionnaire-based cross-sectional survey was conducted among healthcare professionals (HCPs) and patients/caregivers.

9.1 Study design

9.1.1 Content

The study included two distinct questionnaires designed to assess 1) HCPs (neurologists treating patients with MS and MS specialist nurses) knowledge in relation to their role in counselling and on-

going management of patients who are receiving Mayzent treatment and 2) knowledge of patients who are receiving Mayzent or their caregivers in relation to their treatment.

Survey questions for HCPs and patients/caregivers were included to cover the important, identified or potential, risks of siponimod, which 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 (BCC)
- 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 (other than BCC)
    - Reproductive toxicity
    - Unexpected neurological or psychiatric symptoms/signs (e.g., PRES, ADEM, Atypical MS Relapses)

Each questionnaire included an initial set of screening questions to confirm eligibility. Following this the HCP questionnaire comprised a total of 30 questions (two focused on the receipt of educational materials resulting in 28 questions evaluating knowledge). The patient/caregiver questionnaire included a total of 19 questions (1 focused on the receipt of educational materials resulting in 18 questions evaluating knowledge).

Some questions required selection of a single response, while others required selection of multiple responses. Correct responses to multiple response questions have been determined in one of three ways, according to the level of risk associated with incorrect responses (incorrect response options that were close to or closely related to the correct responses were included to ensure a robust test of knowledge), in order to be clinically meaningful. Where the incorrect response options posed no additional risk (for example, additional tests being conducted prior to initiation), selection of <u>all</u> correct responses was considered correct. For questions where incorrect responses indicated potential for inappropriate use of Mayzent the additional criteria of having to select all correct responses <u>with none of the incorrect responses</u> was applied. For some questions for patients/caregivers, the proportion who selected <u>at least one</u> correct response has been considered acceptable.

Both the HCP and patient/caregiver surveys were designed to take fifteen minutes to complete. The average completion time in practice for the HCP survey was 14 minutes and for the patient/caregiver survey was 11 minutes.

The survey is approved by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). In some countries, as per country regulations Health Authority and/or Ethics Committee submissions/ notifications were required. Based on the country prerequisites relevant actions were taken. Details of the country submissions/ notifications have been provided in the below table (Table 9-1).

Table 9-1 Country submissions/notifications to Health Authority

	Submissions/Notification to Health Authority
Country	
Canada	HA Submission/ notifications not required. EC approval received
Croatia	Notification to HA on 14 Oct 2022. EC acknowledgement received
Denmark	HA and EC Submission/ notifications not required
Germany	Notification to HA on 02 May 2022*
Netherlands	Submission/ notifications not required
Spain	HA Submission/ notifications not required. EC approval received
Sweden	HA Submission/ notifications not required. EC acknowledgement received

* There was a delay in notifying the German HA and the survey was initiated prior to the notification. The MAH took remedial action by notifying the BfaRM and other corresponding HA bodies.

9.2 Setting

The survey was administered in Canada and six European markets where Mayzent (siponimod) had been available and reimbursed for at least six months: Germany, Netherlands, Spain, Croatia, Sweden and Denmark.

Table 9-2 Dates of Mayzent (siponimod) commercialization and reimbursement

Country	Mayzent launch date	RMP material distribution date	Date of Mayzent reimbursement	Study start date
Canada	04/2020	22/09/2020	10/2021	17/04/2025
Croatia	15/11/2020	Initial: 07/10/2020 Last: 25/10/2022	01/11/2020	11/11/2022
Denmark	26/01/2021	23/06/2021	01/02/2021	26/02/2023
Germany	15/02/2020	17/02/2020	15/02/2020	06/12/2021
Netherlands	25/03/2020	18/12/2020	01/01/2021	02/12/2021
Spain	03/02/2021	Initial: 09/04/2021 Last: 28/12/2022	01/04/2021	12/04/2023
Sweden	15/04/2020	Initial: 15/04/2020 Last: 16/10/2023	03/07/2020	13/07/2023

In some markets, educational materials were distributed more than once due to updated versions of the RMP and/or educational materials.

9.3 Subjects

The sample comprises HCPs (physicians treating MS and MS specialist nurses) and patients/caregivers.

9.3.1 Physician eligibility criteria and recruitment

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 three 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,
    - Have prescribed Mayzent (siponimod) in at least one SPMS patient.

It should be noted that there was an error in the survey programming that was identified after the start of data collection for HCPs in DE and NL. The eligibility criteria had been incorrectly set to require higher numbers of RRMS and SPMS patients in the past three months. This was corrected and adjusted to align with the protocol as below:

- From at least 20 RRMS patients in the last three months to at least one RRMS patient
- From at least three SPMS patients in the last three months to at least one SPMS patient

Four HCPs in DE and seven HCPs in NL who had previously failed the eligibility check were reinvited to the survey. Therefore, there was no impact on the data collected, and no sample bias was introduced as a result of this error.

All HCPs were recruited exclusively via established healthcare professional panels that are maintained for market research purposes through a third-party recruitment provider; no HCPs were recruited from Novartis lists. Healthcare professionals in the panel have opted-in for market research, and all members are validated at registration to confirm their identity. HCPs who were deemed potentially eligible based on their profile in the panel (e.g. country, specialty) were sent an email to introduce the study and provided a link to the online survey, with random selection applied and no additional selection criteria. The Healthcare professional was asked to provide informed consent at the start of the online survey and then answered the screening questions to confirm their eligibility to participate. If the HCP met the eligibility criteria, the main survey was initiated. Up to three reminders were sent to HCPs who had not started or fully completed the survey, and the survey remained open until the required number of completed surveys in each market was achieved.

9.3.2 Nurse eligibility criteria and recruitment

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 personally managed a patient that has been prescribed Mayzent (siponimod) within three 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 one SPMS patient.

The recruitment methods and processes were the same for nurses as those for physicians.

9.3.3 Patient (or caregiver of patient meeting this profile) eligibility criteria and recruitment

To be eligible to enroll and complete the survey patients must be over 18 years old and have received Mayzent (siponimod) to treat their MS within the last three months. Caregivers must be caring for an adult patient who has received Mayzent (siponimod) to treat their MS within the last three months.

Patients/caregivers in EU were recruited via direct recruitment methods using patient panels and recruiter databases. In Canada, four patients were recruited via HCP referrals, and one from a patient panel. Those deemed potentially eligible based on their profile in the panel (e.g. country, diagnosed condition) were sent an email to introduce the study and provide a link to the online survey, with random selection applied to panel members and no additional selection criteria. Patients/caregivers recruited via HCP referrals were also sent an email to introduce the study and provide a link to the online survey. The patient/caregiver was asked to provide informed consent at the start of the online survey and then answered the screening questions to confirm their eligibility to participate. If patients/caregivers met the eligibility criteria, the main survey was initiated. Up to three reminders were sent to patients/caregivers who had not started or not fully completed the survey, and the survey remained open until the required number of completed surveys in each market was achieved. No paper versions of the survey were required as all patients/caregivers were able to complete the survey online.

9.3.4 Honoraria

9.4 Variables

The following table (Table 9-4) provides a comprehensive mapping of each survey question, associated question numbers, treatment stage and safety area included in the study to the corresponding identified or potential risk(s) from the RMP, as defined in Section 7.

Table 9-4 List of HCP & Patient/Caregiver questions

	HCP questions	
Number	**Question Text**	**Key message (section 7 reference)**

Receipt of materials		
H – Q1	Have you received the healthcare professional's checklist which outlines the considerations before, during and after treatment with Mayzent (siponimod)?	n/a
H – Q2	Have you received patient reminder cards for Mayzent (siponimod)?	n/a
Patient identification and eligibility		
H - Q3	Prior to commencing treatment with Mayzent (siponimod), the CYP2C9 genotype of every patient should be determined	Message 2
H - Q4	Which of the following maintenance doses is correct for the initiation of Mayzent (siponimod) for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?	Message 2
Initiation and first dose		
H - Q5	Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?	Message 5
H – Q6	When initiating treatment with Mayzent (siponimod) 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	Message 4
H - Q7	When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?	Message 9
H - Q8	For which of the following medications/therapies is co-administration not recommended for Mayzent (siponimod)?	Message 5
H - Q9	Caution should be taken when switching to Mayzent (siponimod) from other disease modifying therapies due to the risk of additive immune system effects	Message 5
H - Q10	Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?	Message 5
Titration		
H - Q11	An up-titration scheme is required for Mayzent (siponimod). Please indicate the number of days this scheme takes to complete.	Message 4
H - Q12	When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?	Message 4
H - Q13	The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are:	Message 4
H - Q14	What steps need to be taken if a dose is missed for more than one day during the first 6 days treatment initiation?	Message 3
H - Q15	Have you counselled your patients on the importance of taking their daily dose of Mayzent (siponimod), during both titration and maintenance phases of treatment?	Message 3, 4
Initiation and first dose		
H - Q16	For which type/s of patients is Mayzent (siponimod) not recommended?	Message 4, 5, 6
H - Q17	How many hours should a patient with sinus bradycardia, 1st /2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?	Message 4

H - Q18	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?	Message 4
H - Q19	Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other specialized MS center for FDM?	n/a
During treatment		
H - Q20	For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?	Message 6
H - Q21	At what time after starting treatment should a full ophthalmologic evaluation be performed?	Message 6
H - Q22	Patients receiving Mayzent (siponimod) should be counselled to report signs and symptoms of infection immediately to their prescriber	Message 5
H - Q23	Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection	Message 9
H - Q24	You should check varicella zoster virus antibody status in patients receiving Mayzent (siponimod) without a healthcare professionally confirmed history of chicken pox	Message 5
H - Q25	Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?	Message 5
H - Q26	What action should be taken if a patient reports serious infection during treatment on Mayzent (siponimod)?	Message 5
H - Q27	After stopping treatment, for how long does Mayzent (siponimod) remain in the blood?	Message 5
H - Q30	What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?	Message 8
Risk of pregnancy		
H - Q28	For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod)? For at least…	Message 7
H - Q29	For patients who become pregnant during treatment, what is the correct approach from the options below?	Message 7

	Patient/caregiver questions	
Number	**Question Text**	**Key message (section 7 reference)**
Receipt of materials		
P – Q1	Have you / the person you are caring for with SPMS received any education materials for Mayzent (siponimod)?	n/a
Patient identification and eligibility		
P - Q2	For what reasons will the doctor do a blood test before you get ready for your treatment with Mayzent (siponimod)?	Message 5

P - Q3	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)?	Message 5
P - Q4	For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with Mayzent (siponimod)?	Message 6
P - Q5	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)	Message 4
P - Q6	When, if at all, may your doctor want to conduct a skin examination?	Message 9
Initiation and first dose		
P - Q7	At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask you to stay in the clinic after taking the first dose so that your blood pressure and pulse can be monitored?	Message 4
P - Q8	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?	Message 4
Titration		
P - Q9	Are you aware that there is a period of titration/ up-dosing at the start of treatment with Mayzent (siponimod).	Message 4
P - Q10	For how many days is the titration / up-dosing schedule (pack)?	Message 4
P - Q11	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	Message 3, 4
During treatment		
P - Q12	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)?	Message 6
P - Q13	What are the symptoms that may mean you are experiencing an infection including brain infection?	Message 5, 8
P - Q14	What are the symptoms that may mean you may be experiencing impaired liver function?	Message 5
P - Q15	Which skin conditions, if any, should be reported immediately to your doctor?	Message 9
P - Q16	You should avoid exposure to sunlight without protection while on Mayzent (siponimod).	Message 9
P - Q19	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 Mayzent (siponimod) treatment be interrupted before you need to contact your doctor and reinitiate treatment with a new starter pack?	Message 3

Risk of pregnancy		
P – Q17	*(Female patients of childbearing age only)* You must avoid getting pregnant while on Mayzent (siponimod).	Message 7
P - Q18	*(Female patients of childbearing 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?	Message 7

9.5 Data sources and measurement

Data sources included:

- 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

9.6 Bias

The potential for selection bias of a participant in a survey is an inherent bias/limitation to any study based on volunteer participation. HCPs were recruited via databases and patient/caregivers were recruited primarily 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 surveys. However, this is minimized by inviting a random sample from the database, rather than targeting specific individuals. For both HCPs and patients/caregivers profiling questions within the survey are included to ensure the sample represents the wider population.

There is also potential for recall bias, based on HCPs and patient caregivers thinking back over time when answering the survey, and not directly referring to the educational materials.

9.7 Study size

The total number of completed surveys for HCPs and patients/caregivers in each country is shown in Table 9-5. Although the protocol specified a patient/caregiver sample of n=115, data from three additional patients/caregivers have been included, from individuals who had already commenced the survey when the target sample was reached. They were permitted to complete the survey and their data are included.

Table 9-5 Total achieved sample

	Country							
	DE	NL	HR	ES	SE	DK	CA	**Total**
HCP sample	70	25	30	65	5	5	20	**220**
Patient/ caregiver sample	35	18	15	35	5	5	5	**118**

9.8 Data transformation

Not applicable

9.9 Statistical methods

9.9.1 Main summary measures

As per the protocol, the statistical analysis for this survey was descriptive in nature. For continuous variables, counts, means (with standard deviations), medians and ranges are provided. For categorical variables, frequencies and percentages (with 95% confidence intervals) are provided

9.9.2 Main statistical methods

Not applicable

9.9.3 Missing values

Not applicable. All survey questions required an answer, with “None” or “I don’t know” options available where relevant.

9.9.4 Sensitivity analyses

Not applicable

9.9.5 Amendments to the statistical analysis plan

Not applicable

9.10 Quality control

Two modes of data cleaning were put in place. The first looked at response patterns within the data (for instance respondents always selecting the top response across questions or repeating a pattern of responses (for example first option / second option / third option / fourth option)). Mean occurrences of the number of patterns identified within the overall data set allowed identification of respondents with a mean number of patterns sitting outside one standard deviation of this. The second mode focused on length of interview. A mean survey length was established and again respondents with a survey length sitting outside one standard deviation of this were identified.

Following data checks no respondents were removed from the data set for speeding and patterned responses. Questions with open numeric responses were quality checked to remove any outlier responses.

10 Results

10.1 Participants

Table 10-1 and Table 10-2 show the total number of potential participants who were invited to participate in the HCP survey and the patient/caregiver survey respectively, for each market. Additionally, the number of non-responders, and the number of ineligible and eligible participants is also shown.

Table 10-1 HCPs invited and participating in the survey

	Invited		**Eligibility**	
	Total HCPs invited	Non-responders	Not meeting eligibility criteria	Met eligibility criteria and completed survey

DE	1065	955 (89.7%)	40 (3.8%)	70 (6.6%)
NL	215	173 (80.5%)	17 (7.9%	25 (11.6%)
HR	85	51 (60.0%)	4 (4.7%)	30 (35.3%)
ES	883	784 (88.8%)	34 (3.8%)	65 (7.4%)
SE	110	104 (94.5%)	1 (0.9%)	5 (4.5%)
DK	140	114 (81.4%)	21 (15.0%)	5 (3.6%)
CA	76	56 (73.7%)	0 (0.0%)	20 (26.3%)
Total	**2574**	**2237 (86.9%)**	**117 (4.5%)**	**220 (8.5%)**

Table 10-2 Patients/caregivers invited and participating in the survey

	Invited		**Eligibility**	
	Total patient/ caregivers invited	Non-responders	Not meeting eligibility criteria	Met eligibility criteria and completed survey
DE	2395	2283 (95.3%)	82 (3.4%)	35 (1.5%)
NL	303	257 (84.8%)	28 (9.2%)	18 (5.9%)
HR	421	388 (92.2%)	18 (4.3%)	15 (3.6%)
ES	287	240 (83.6%)	12 (4.2%)	35 (12.2%)
SE	29	16 (55.2%)	8 (27.6%)	5 (17.2%)
DK	37	29 (78.4%)	3 (8.1%)	5 (13.5%)
CA	400	374 (93.5%)	21 (5.3%)	5 (1.25%)
Total	**3872**	**3595 (92.8%)**	**172 (4.4%)**	**118 (3.0%)**

10.2 Descriptive data

Table 10-3 shows HCPs were from a mix of practice settings. The number of patients with relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) seen by physicians in the last three months ranged from 2 to 600 and 1 to 350 respectively (with outliers excluded).

Table 10-3 Sample demographics (HCPs)

	Country							
	Total	DE	NL	HR	ES	SE	DK	CA
N =	220	70	25	30	65	5	5	20
S2A. Specialty								
MS specialist nurse	59 (27%)	18 (26%)	5 (20%)	9 (30%)	19 (29%)	1 (20%)	1 (20%)	6 (30%)
Neurologist	161 (73%)	52 (74%)	20 (80%)	21 (70%)	46 (71%)	4 (80%)	4 (80%)	14 (70%)
S3. Practice hospital type								
Hospital Only	116 (53%)	21 (30%)	22 (88%)	27 (90%)	32 (49%)	-	4 (80%)	10 (50%)
Hospital and Office	84 (38%)	32 (46%)	2 (8%)	3 (10%)	33 (55%)	5 (100%)	-	9 (45%)
Private office only	20 (9%)	17 (24%)	1 (4%)	-	-	-	1 (20%)	1 (5%)
S3a. Primary hospital type (hospital-based HCPs only)								
Teaching/University hospital	138 (69%)	41 (77%)	1 (4%)	13 (43%)	60 (92%)	3 (60%)	4 (100%)	16 (84%)
Public non-teaching (general) hospital	59 (30%)	10 (19%)	23 (96%)	17 (57%)	4 (6%)	2 (40%)	-	3 (16%)
Private hospital	3 (2%)	2 (4%)	-	-	1 (2%)	-	-	-
S5. Number of patients treated with relapsing remitting multiple sclerosis in last three months (excl. outliers)								
1-49	84 (39%)	19 (28%)	10 (40%)	22 (76%)	26 (42%)	3 (60%)	3 (60%)	1 (5%)
50-149	80 (37%)	33 (49%)	12 (48%)	7 (24%)	19 (31%)	2 (40%)	2 (40%)	5 (25%)
150+	50 (23%)	16 (24%)	3 (12%)	-	17 (27%)	-	-	14 (70%)
Min. (no. patients)	2	10	4	3	6	20	2	40
Max (no. patients)	600	500	200	100	600	80	80	500
Mean (no. patients)	100	103	67	30	121	48	42	198
Standard deviation	112	102	51	36	140	24	30	121
Median	60	63	50	11	60	45	40	175

S6. Number of patients treated with Secondary progressive multiple sclerosis in last three months (excl. outliers)								
1-49	154 (72%)	46 (67%)	21 (88%)	29 (100%)	38 (59%)	5 (100%)	5 (100%)	10 (53%)
50-149	46 (21%)	17 (25%)	3 (13%)	-	18 (28%)	-	-	8 (42%)
150-250	15 (7%)	6 (9%)	-	-	8 (13%)	-	-	1 (5%)
Min. (no. patients)	1	3	4	1	2	20	1	5
Max (no. patients)	350	350	100	20	350	30	30	150
Mean (no. patients)	44	51	23	6	63	23	16	47
Standard deviation	61	62	24	6	81	4	12	38
Median	20	30	18	3	29	23	12	40
S7. SPMS patients on Mayzent to date (excl. outliers)								
1-20	161 (75%)	44 (64%)	24 (100%)	28 (97%)	42 (66%)	4 (80%)	3 (60%)	16 (84%)
21-49	30 (14%)	14 (20%)	-	1 (3%)	9 (14%)	1 (20%)	2 (40%)	3 (16%)
50+	24 (11%)	11 (16%)	-	-	13 (20%)	-	-	-
Min. (no. patients)	1	1	1	1	1	1	1	2
Max (no. patients)	300	200	8	30	300	25	30	40
Mean (no. patients)	23	27	3	5	39	7	14	13
Standard deviation	45	40	2	6	66	10	13	12
Median	7	12	2	3	15	5	10	10

Table 10-4 shows the profile of patients/caregivers (with outliers excluded), and indicates in most cases, patients completed the survey themselves (77%). The average age of MS patients was 46 years, and a higher proportion were female (59%) than male (40%). Other profiling questions were included to ensure a balanced and representative sample.

Table 10-4 Sample demographics (Patient/Caregiver)

	Country							
	Total	DE	NL	HR	ES	SE	DK	CA
N =	118	35	18	15	35	5	5	5
S2A. Specialty								
Patient	91 (77%)	31 (89%)	10 (56%)	9 (60%)	28 (80%)	3 (60%)	5 (100%)	5 (100%)
Caregiver	27 (23%)	4 (11%)	8 (44%)	6 (40%	7 (20%)	2 (40%)	-	-

S3. Age of MS patients								
18-25	1 (1%)	1 (3%)	-	-	-	-	-	-
26-35	16 (14%)	12 (34%)	1 (6%)	-	2 (6%)	-	1 (20%)	-
36-45	39 (33%)	9 (26%)	5 (28%)	8 (53%)	10 (29%)	4 (80%)	2 (40%)	1 (20%)
46-55	46 (39%)	12 (34%)	9 (50%)	4 (27%)	17 (49%)	-	2 (40%)	2 (40%)
56+	17 (14%)	2 (6%)	3 (17%)	3 (20%)	6 (17%)	1 (20%)	-	2 (40%)
Min.	25	25	26	38	27	41	35	43
Max	71	55	63	59	63	71	49	64
Mean	46	42	48	45	48	47	42	55
Standard deviation	9	9	9	10	8	13	6	8
Median	47	43	49	38	47	42	40	55
S4. Gender of MS patients								
Male	47 (40%)	14 (40%)	8 (44%)	2 (13%)	17 (49%)	3 (60%)	-	3 (60%)
Female	70 (59%)	21 (60%)	10 (56%)	13 (87%)	17 (49%)	2 (40%)	5 (100%)	2 (40%)
Non-binary	-	-	-	-	-	-	-	-
Prefer not to say	1 (1%)	-	-	-	1 (3%)	-	-	-
S5. Employment status of MS patients								
Full time employment	43 (36%)	14 (40%)	5 (28%)	3 (20%)	15 (43%)	4 (80%)	-	2 (40%)
Part time employment	28 (24%)	7 (20%)	4 (22%)	2 (13%)	10 (29%)	-	5 (100%)	-
Not employed	47 (40%)	14 (40%)	9 (50%)	10 (67%)	10 (29%)	1 (20%)	-	3 (60%)
S6. Time since MS diagnosis								
0-10 Years	70 (60%)	24 (69%)	9 (50%)	4 (27%)	26 (76%)	4 (80%)	3 (60%)	-
11-20 Years	33 (28%)	7 (20%)	6 (33%)	8 (53%)	6 (18%)	1 (20%)	2 (40%)	3 (60%)
21-30 Years	11 (9%)	2 (6%)	3 (17%)	3 (20%)	2 (6%)	-	-	1 (20%)
31-39 Years	4 (3%)	2 (6%)	-	-	1 (3%)	-	-	1 (20%)
Min.	0	1	2	1	0	1	7	18
Max	39	37	25	24	39	15	14	35
Mean	10.7	10.3	11.7	14.5	7.8	5.0	10.4	23.4

Standard deviation	8.4	9.6	6.5	6.9	6.6	5.7	2.7	7.0
Median	8.0	6.0	11.0	14.0	4	3	10	20
S7. Time since SPMS diagnosis								
0-10 Years	110 (93%)	32 (91%)	16 (89%)	13 (87%)	35 (100%)	5 (100%)	5 (100%)	4 (80%)
11-20 Years	8 (7%)	3 (9%)	2 (11%)	2 (13%)	-	-	-	1 (20%)
Min	0	1	1	1	0	1	1	2
Max	20	18	12	20	8	8	4	11
Mean	3.7	3.9	3.8	5.8	2.3	3.0	2.8	6.8
Standard deviation	3.5	4.3	3.3	4.7	1.6	2.8	1.3	3.7
Median	3	3	3	5	2	2	3	8
S8. Treatment received prior to Mayzent (siponimod)								
Aubagio (Teriflunomide)	29 (25%)	7 (20%)	4 (22%)	1 (7%)	14 (40%)	1 (20%)	2 (20%)	-
Avonex (Interferon beta 1a IM)	13 (11%)	8 (23%)	-	2 (13%)	2 (6%)	-	-	1 (20%)
Betaferon/Extavia (Interferon beta 1b SC)	17 (14%)	6 (17%)	3 (17%)	1 (7%)	7 (20%)	-	-	-
Copaxone (Glatiramer Acetate)	18 (15%)	5 (14%)	5 (28%)	2 (13%)	2 (6%)	2 (40%)	-	2 (40%)
Gilenya (Fingolimod)	22 (19%)	4 (11%)	2 (11%)	1 (7%)	11 (31%)	2 (40%)	-	2 (40%)
Lemtrada (Alentuzumab)	18 (15%)	9 (26%)	3 (17%)	-	4 (11%)	-	2 (40%)	-
Mavenclad (Cladribine)	14 (12%)	4 (11%)	5 (28%)	-	4 (11%)	-	-	1 (40%)
Ocrevus (Ocrelizumab)	25 (21%)	10 (29%)	2 (11%)	6 (40%)	6 (17%)	-	1 (20%)	-
Rebif (Interferon beta 1a SC)	23 (19%)	7 (20%)	1 (6%)	2 (13%)	8 (23%)	-	1 (20%)	4 (80%)
Tecfidera (Dimethyl Fumarate)	20 (17%)	9 (26%)	3 (17%)	1 (7%)	3 (9%)	1 (20%)	2 (40%)	1 (20%)
Tysabri (Natalizumab)	20 (17%)	13 (37%)	2 (11%)	-	2 (6%)	-	2 (40%)	1 (20%)
Other	12 (10%)	6 (17%)	1 (6%)	3 (20%)	2 (6%)	-	-	-

10.3 Outcome data

Not applicable

10.4 Main results

10.4.1 Receipt of educational materials

HCPs were asked about receipt of two specific educational materials: the prescriber's checklist and the patient reminder card. HCPs in NL were not asked about the patient reminder card as this is not in use in this market. A total of 85% (n=186/220) of HCPs recall receiving the prescriber's checklist and 75% (n=146/195) had received the patient reminder cards.

56% of patients/caregivers recalled receiving educational materials for Mayzent, with a further 16% unsure.

10.4.2 Treatment stage analysis

An overview of the proportion of correct responses from HCPs across all questions included in the survey is presented in Figure 1. Among HCPs, 75% (21/28) of the survey questions had 50% or more correct responses. This included 12/28 questions that had 70% or more correct responses and these were all questions that required a single correct response. Furthermore, 7/28 questions demonstrated a strong level of knowledge, with 90% or more of HCPs responding correctly. There were also 9/28 questions with 50–69% correct responses (4 with multiple correct responses, and 5 with a single correct response) and 7/28 questions with less than 50% correct responses (4 with multiple correct responses and 3 with a single correct response).

Among HCPs who recall receiving the educational materials there are also 12/28 questions with 70% or more correct responses, including 8/28 achieving 90% or more, and one additional question scoring over 50%, resulting in 10/28 questions with 50-69% correct responses and 6/28 with less than 50%.

Of the 8 questions with multiple correct responses that failed to reach the 70% threshold for success, 6 of these had one or more separate correct responses that were selected by 70% of more HCPs, indicating HCPs have good knowledge of these topics but failed to meet the criteria for success defined as selecting all correct responses.

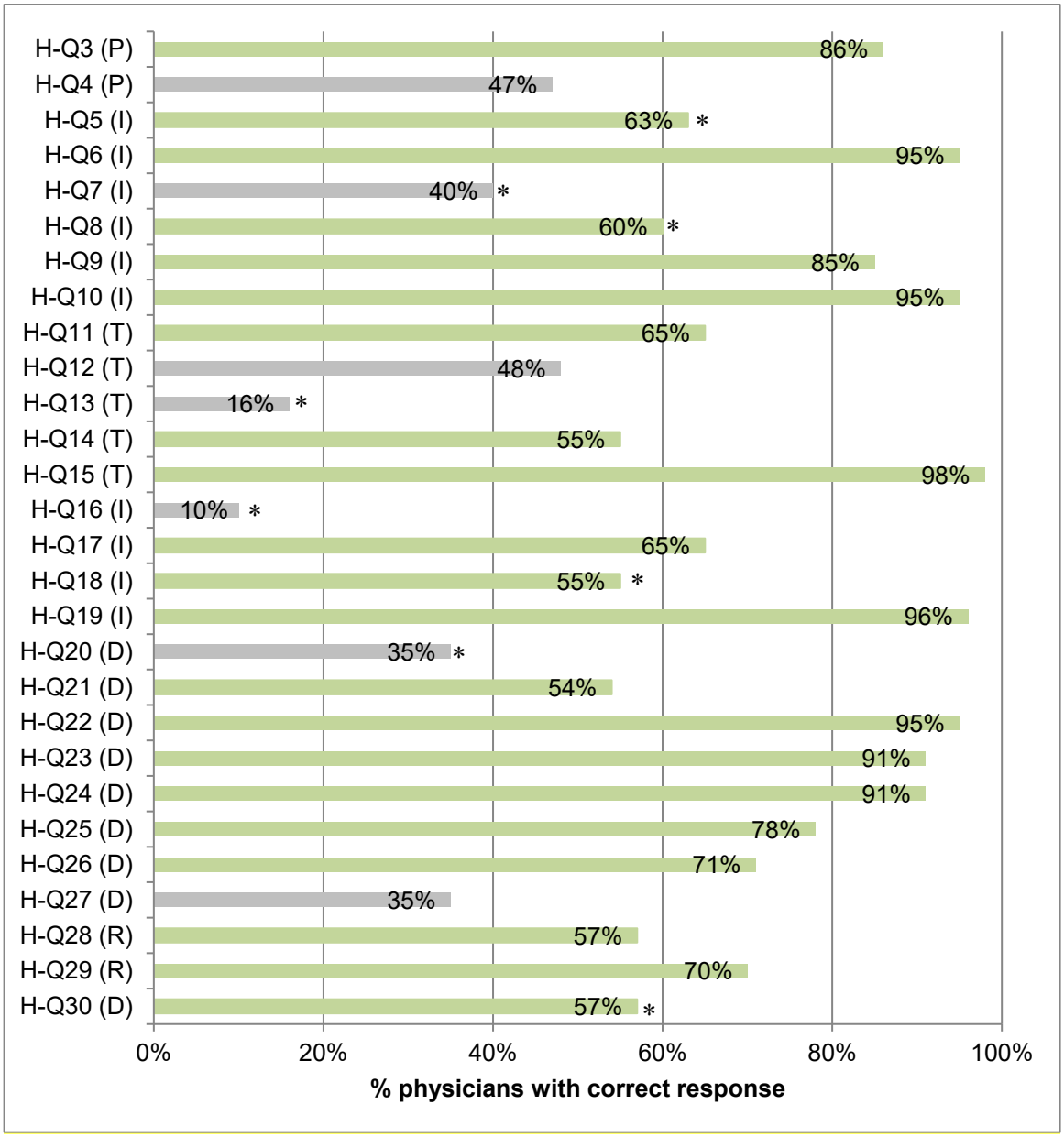
Similarly, Figure 2 presents the results for patients/caregivers. In the patient/caregiver survey, 6/18 questions had 70% or more correct responses (2 with multiple correct responses, and 4 with a single correct response), with only one question achieving 90% or higher. Additionally, 5/18 questions had 50–69% correct responses (1 with multiple correct responses, and 4 with a single correct response) and 7/18 questions had less than 50% correct responses (4 with multiple correct responses, and 3 with a single correct response).

Among patients/caregivers who recall receiving the educational materials, there are 8/18 questions with 70% or more correct responses, including one question over 90%. There are 5/18 questions with 50-69% correct responses and 5/18 questions with less than 50% correct.

Of the 5 questions with multiple correct responses that failed to reach the 70% threshold for success, none of these had any separate correct responses that were selected by 70% of more.

A review of these questions and possible confounders is provided in the results and discussion sections.

Figure 1. Percentage of clinically meaningful correct responses across all questions (HCP)

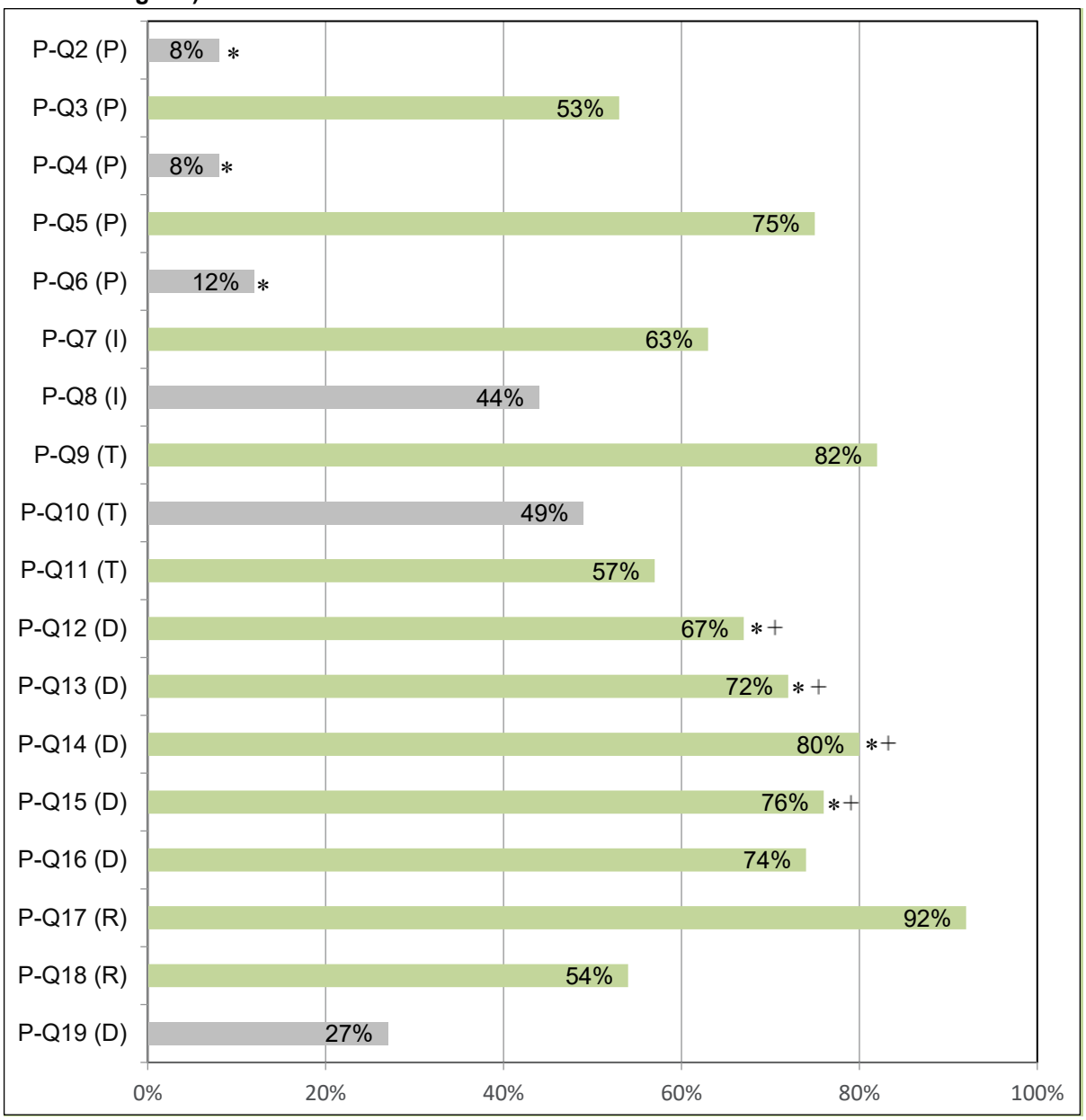


Note – Screener questions (S1-6a) and materials receipt /awareness / use questions (Q1-2) not included

Note – Letters in brackets after question numbers refer to the treatment stage: P- Patient identification and eligibility; I – Initiation and first dose; T – Titration; D – During treatment; R – Risk of pregnancy

*Note – * denotes questions with more than one correct response*

Figure 2. Percentage of clinically meaningful correct responses across all questions (Patient/Caregiver)



Note – Screener questions (S0a-8) and materials receipt /awareness / use questions (Q1) not included

Note – Letters in brackets after question numbers refer to the treatment stage: P- Patient eligibility; I – Initiation; T – Titration; D – During treatment; R – Risk of pregnancy

*Note – * denotes questions with more than one correct response, + denotes questions where the response of selecting at least one correct response has been considered as clinically meaningful*

Figures in the remainder of this report provide an analysis of the survey results by treatment stage. For each treatment stage the percentage of correct answers is presented, grouped into respondent type, HCP or patient/caregivers, with correct responses at least 50% representing the majority highlighted in green, and below 50% highlighted in grey.

For questions where the protocol threshold of 70% correct response is not achieved, further detail and discussion is provided on the pattern of incorrect response.

10.4.3 Receipt of materials (HCP)

Figure 3 shows HCP responses to each question pertaining to the assessment of materials being received. The responses showed that over 70% of HCPs received both the professional checklist, outlining the considerations before, during and after treatment, and the patient reminder cards for Mayzent (siponimod). It should be noted that the question relating to patient reminder cards was not asked in Netherlands as these are not in use in this market.

Figure 3. Receipt of materials – HCP responses

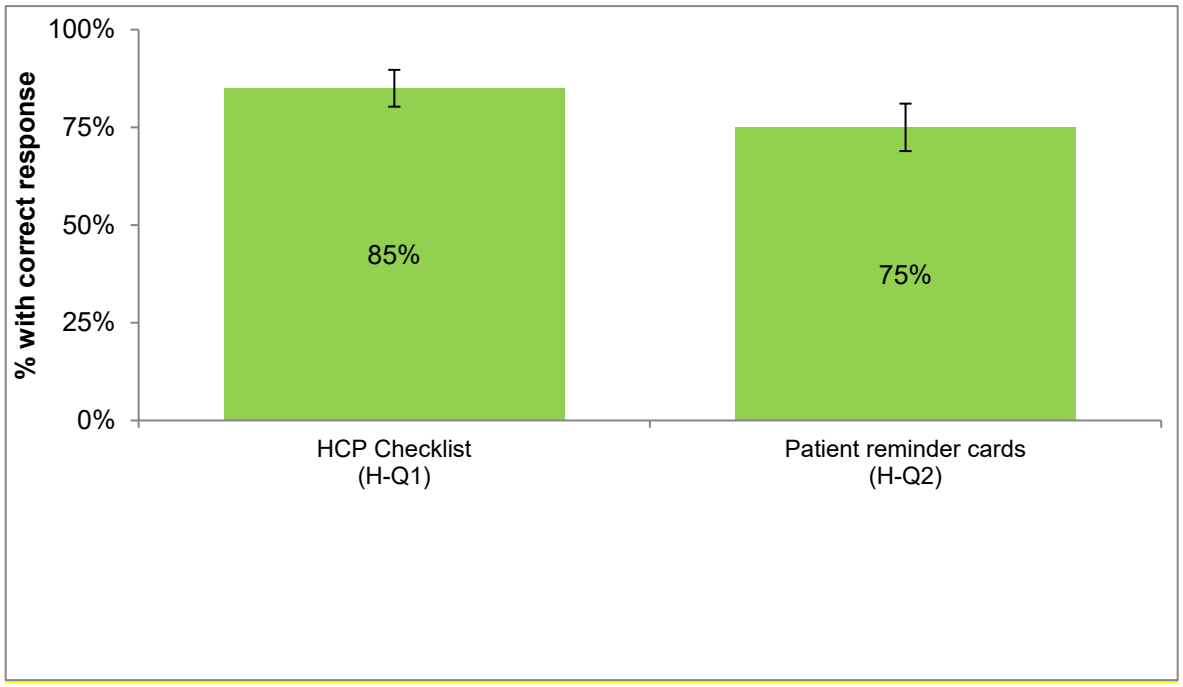


Table 10-5 Detailed response to H-Q1 – Have you received the healthcare professional's checklist which outlines the considerations before, during and after treatment with Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	186	60	21	28	54	5	4	14
	85%	86%	84%	93%	83%	100%	80%	70%
No	34	10	4	2	11	0	1	6
	15%	14%	16%	7%	17%	0%	20%	30%

Table 10-6 Detailed response to H-Q2 – Have you received patient reminder cards for Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**195**	**70**	n/a	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	n/a	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	146	57	n/a	24	50	5	4	6
	75%	81%	n/a	80%	77%	100%	80%	30%
No	49	13	n/a	6	15	0	1	14
	25%	19%	n/a	20%	23%	0%	20%	70%

10.4.4 Patient identification and eligibility (HCP)

Figure 4 shows HCP responses to each question pertaining to the identification of appropriate patients for prescribing. The results showed greater knowledge with the predetermining of the CYP2C9 genotype with over 70% of HCPs answering correctly in comparison to less than 50% correct responses for the correct maintenance dose for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3.

Figure 4. Patient identification and eligibility – HCP responses

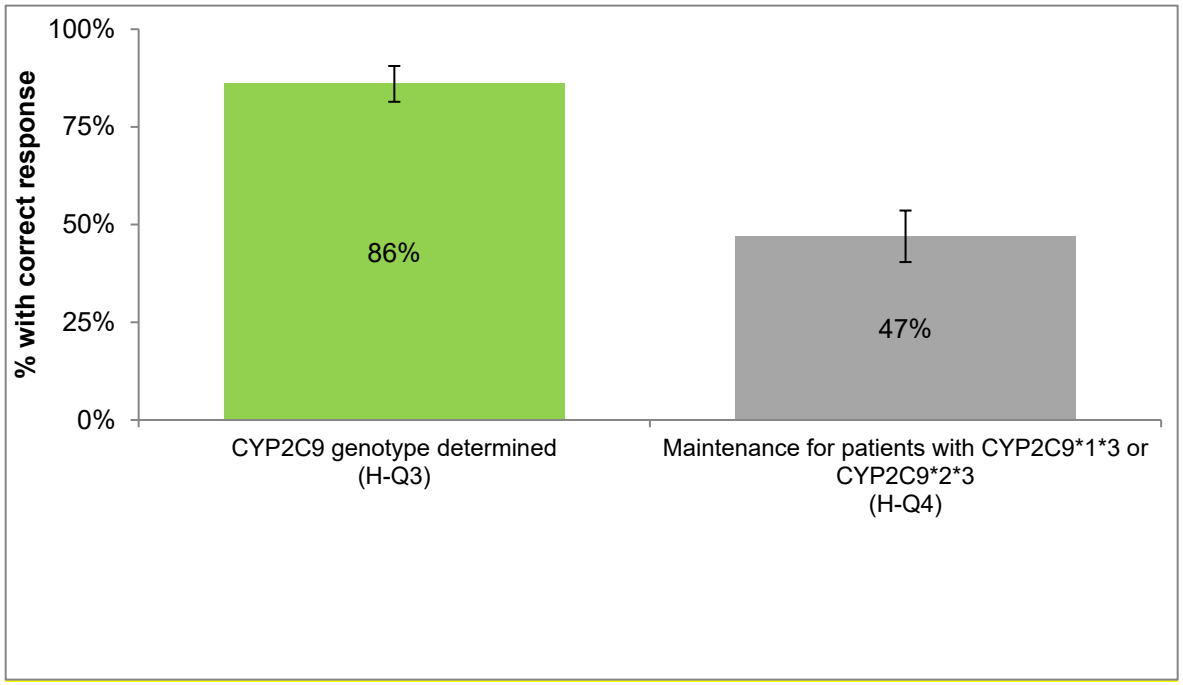


Table 10-7 Detailed response to H-Q3 – Prior to commencing treatment with Mayzent (siponimod), the CYP2C9 genotype of every patient should be determined

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	190	58	21	28	56	4	3	20
	86%	83%	84%	93%	86%	80%	60%	100%
No	5	1	1	0	3	0	0	0
	2%	1%	4%	0%	5%	0%	0%	0%
I don't know/ I am not sure	25	11	3	2	6	1	2	0
	11%	16%	12%	7%	9%	20%	40%	0%

Green cells indicate correct response.

Table 10-8 shows responses for H-Q4 (correct maintenance dose for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3). There was only one correct answer for this question (1 mg), which was selected by 47% of HCPs, and this was the most frequently selected answer option. 25% selected 2mg, which is the maintenance dose for other types of patients.

Table 10-8 Detailed response to H-Q4 – Which of the following maintenance doses is correct for the initiation of Mayzent (siponimod) for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
1 mg	103	30	12	22	23	3	4	9
	47%	43%	48%	73%	35%%	60%	80%	45%
1.25 mg	14	3	0	2	9	0	0	0
	6%	4%	0%	7%	14%	0%	0%	0%
2 mg	56	18	8	6	20	1	0	3
	25%	26%	32%	20%	*31%*	*20%*	0%	*15%*
10 mg	4	4	0	0	0	0	0	0
	2%	6%	0%	0%	0%	0%	0%	0%
I don't know/ I am not sure	43	15	5	0	13	1	1	8
	20%	21%	20%	0%	20%	20%	20%	40%

Green cells indicate correct response.

10.4.5 Initiation and first dose (HCP)

Figure 5 shows HCP responses to each question pertaining to the assessment of initiation steps prior to prescribing Mayzent (siponimod). Responses varied with three questions achieving over 70% correct responses. The remaining three questions showed lower levels of knowledge with between 40% and 63% of HCPs responding correctly.

Figure 5. Initiation and first dose – HCP responses

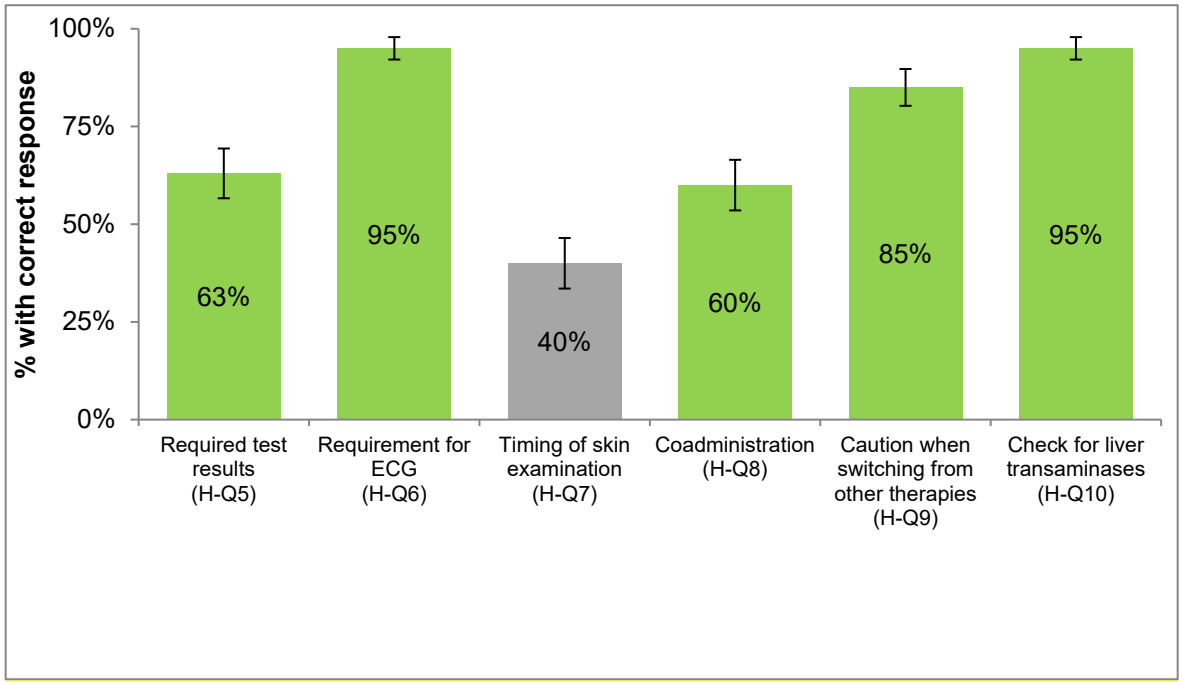


Table 10-9 shows responses for H-Q5, requirements for test results prior to initiation. There were two correct answers to this question (transaminase and bilirubin levels & full blood count), which were selected by 74% and 84% of HCPs respectively, each achieving the required threshold for success, with 63% of HCPs selecting both responses. More than 1 in 5 respondents also selected 'calcium' (22%) and 'glucose' (24%), which are not required for Mayzent initiation, but HCPs may routinely conduct these tests as part of their patient management process.

Table 10-9 Detailed response to H-Q5 – Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Transaminase and bilirubin levels	163	53	14	18	54	2	4	18
	74%	76%	56%	60%	83%	40%	80%	90%
Full blood count	184	58	22	29	48	5	4	18

	84%	83%	88%	97%	74%	100%	80%	90%
Cholesterol	44	15	0	5	22	0	0	2
	20%	21%	0%	17%	34%	0%	0%	10%
Calcium	49	24	0	2	22	1	0	0
	22%	34%	0%	7%	34%	20%	0%	0%
Glucose	52	19	0	7	24	1	0	1
	24%	27%	0%	23%	37%	20%	0%	5%
None of these	2	0	0	0	2	0	0	0
	1%	0%	0%	0%	3%	0%	0%	0%
I don't know/I am not sure	7	3	1	0	3	0	0	0
	3%	4%	4%	0%	5%	0%	0%	0%
Both correct responses (with or without additional responses)	*138*	*46*	*12*	*17*	*42*	*2*	*3*	*16*
	63%	*66%*	*48%*	*57%*	*65%*	*40%*	*60%*	*80%*

Green cells indicate correct responses.

Table 10-10 Detailed response to H-Q6 – When initiating treatment with Mayzent (siponimod) 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

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	209	66	24	29	61	4	5	20
	95%	94%	96%	97%	94%	80%	100%	100%
No	5	3	1	0	1	0	0	5
	2%	4%	4%	0%	2%%	0%	0%	2%
I don't know/ I am not sure	6	1	0	1	3	1	0	0
	3%	1%	0%	3%	5%	20%	0%	0%

Green cells indicate correct response.

Table 10-11 shows responses for H-Q7, relating to the timing of skin examinations. There were two correct answers to this question, which were selected by 59% and 75% of HCPs respectively. 93% selected at least one correct answer, indicating that most HCPs are aware of the need for skin examinations, although only 40% of HCPs selected both correct responses.

Table 10-11 Detailed response to H-Q7 – When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Prior to treatment initiation	129	44	13	21	36	3	3	9
	59%	63%	52%	70%	55%	60%	60%	45%
Every 6-12 months following initiation	165	48	19	25	54	2	4	13
	75%	69%	76%	83%	83%	40%	80%	65%
Not at all	2	0	0	0	0	1	0	1
	1%	0%	0%	0%	0%	20%	0%	5%
I don't know/ I am not sure	13	7	0	2	1	0	1	1
	6%	10%	0%	7%	2%	0%	20%	5%
At least 1 correct response	*205*	*63*	*25*	*28*	*64*	*4*	*4*	*17*
	93%	*90%*	*100%*	*93%*	*98%*	*80%*	*80%*	*85%*
Both correct responses	*89*	*29*	*7*	*18*	*26*	*1*	*3*	*5*
	40%	*41%*	*28%*	*60%*	*40%*	*20%*	*60%*	*25%*

Green cells indicate correct responses.

Table 10-12 shows that responses for H-Q8 (potential drug-drug interactions) were varied. There were two correct answers to this question, which were selected by 29% and 15% of HCPs respectively. However, the MAH acknowledges that the question could be misleading, by asking for medications/therapies not recommended for coadministration, rather than medications that are contraindicated. The materials advise HCPs to take caution if patients are concomitantly treated with anti-neoplastic, immunomodulatory or immunosuppressive therapies, and so the response at Q8 for "all of the above" could also be considered a correct response. Based on these criteria, 60% of HCPs selected a correct response, and the proportion selecting each individual response is 78% for Class Ia and III anti-arrhythmics and 64% for Phototherapy with UV-B radiation or PUVA photochemotherapy.

Table 10-12 Detailed response to H-Q8 - For which of the following medications/therapies is co-administration not recommended for Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Class Ia and III anti-arrhythmics	63	24	2	9	22	2	0	4
	29%	34%	8%	30%	34%	40%	0%	20%
Anti-neoplastics	39	14	2	9	12	0	1	1
	18%	20%	8%	30%	18%	0%	20%	5%

Immunosuppressive or immunomodulatory agents	44	31	4	9	11	1	1	3
	35%	44%	16%	30%	17%	20%	20%	15%
Phototherapy with UV-B radiation or PUVA photochemotherapy	33	13	2	4	9	1	1	3
	15%	19%	8%	13%	14%	20%	20%	15%
All of the above	108	20	17	15	36	2	2	16
	49%	29%	68%	50%	55%	40%	40%	80%
I don't know/I am not sure	17	9	2	2	3	0	1	0
	8%	13%	8%	7%	5%	0%	20%	0%
Both correct responses or 'All of the above'	*132*	*30*	*17*	*18*	*43*	*3*	*2*	*19*
	60%	*43%*	*68%*	*60%*	*66%*	*60%*	*40%*	*95%*

Green cells indicate correct responses.

Table 10-13 Detailed response to H-Q9 – Caution should be taken when switching to Mayzent (siponimod) from other disease modifying therapies due to the risk of additive immune system effects

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	186	52	23	27	59	5	5	15
	85%	74%	92%	90%	91%	10%	100%	75%
No	17	6	2	3	3	0	0	3
	8%	9%	8%	10%	5%	0%	0%	15%
I don't know/ I am not sure	17	12	0	0	3	0	0	2
	8%	17%	0%	0%	5%	0%	0%	10%

Green cells indicate correct response.

Table 10-14 shows responses for H-Q10 (timeframe for checking liver transaminases). There was only one correct answer to this question (6 months), which was selected by 36% of HCPs. However, the question asked, "*within* what time period" and so responses of two months or three months would also be clinically meaningful and not a risk to patient safety, although not fully aligned with the educational materials.

Table 10-14 Detailed response to H-Q10 – Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***

2 months	60	27	9	9	7	1	1	6
	27%	39%	36%	30%	11%	20%	20%	30%
3 months	69	22	9	7	23	1	0	7
	31%	31%	36%	23%	35%	20%	0%	35%
6 months	79	15	6	13	32	3	4	6
	36%	21%	24%	43%	49%	60%	80%	30%
12 months	0	0	0	0	0	0	0	0
	0%	0%	0%	0%	0%	0%	0%	0%
I don't know / I am not sure	12	6	1	1	3	0	0	1
	5%	9%	4%	3%	5%	0%	0%	5%
Any answer within 6 months	*208*	*64*	*24*	*29*	*62*	*5*	*5*	*19*
	95%	*91%*	*96%*	*97%*	*95%*	*100%*	*100%*	*95%*

Green cells indicate correct response.

Figure 6 shows HCP responses to each question pertaining to the assessment of knowledge requirements for first dose monitoring. The responses showed only one question achieved over 70% correct responses and two achieved over 50%. The remaining question highlighted low levels of understanding in relation to patient type(s) not recommended for Mayzent (10%), although this question required selection of multiple correct responses.

Figure 6. Initiation and first dose – HCP responses

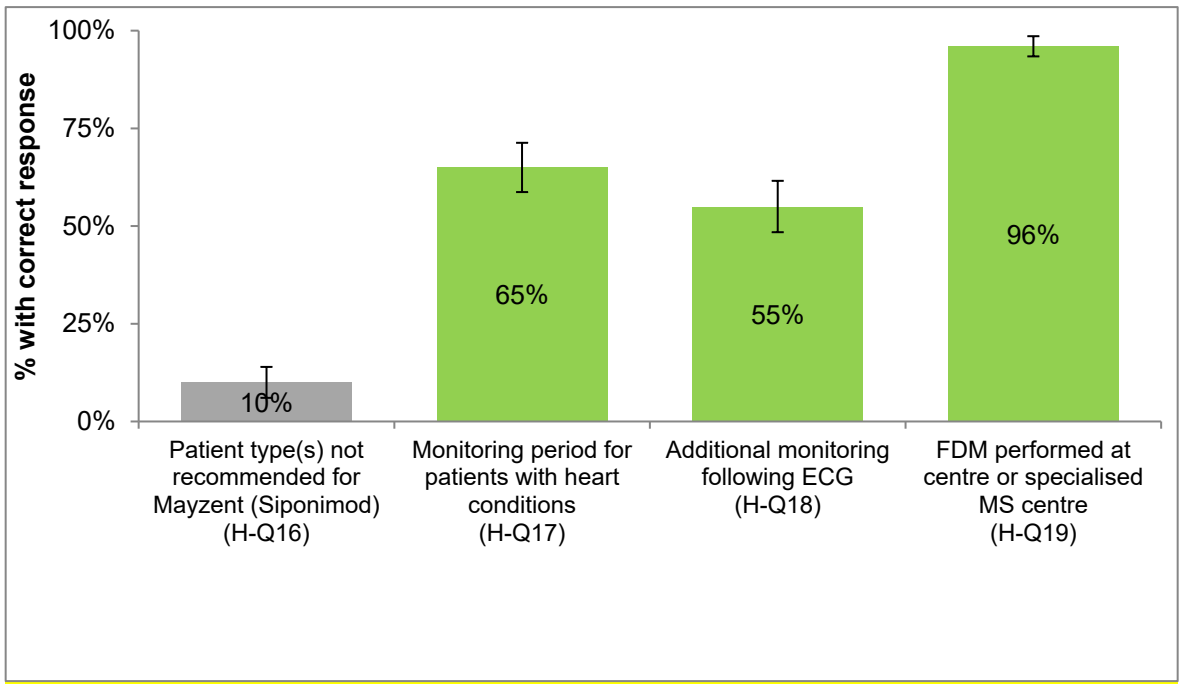


Table 10-15 shows that responses for H-Q16 (contraindications) were varied. There were seven correct answers listed in the protocol, with all selected by less than 70% of HCPs. However, four of these were

selected by between 66% and 68% of HCPs. The educational materials also refer to other medications (e.g. ivabradine or digoxin) which are known to decrease the heart rate, and so 'patients treated with beta-blockers' has also been considered a correct response, due to the bradycardic effect of beta-blockers – this was selected by 32% of HCPs.

Table 10-15 Detailed response to H-Q16 – For which type/s of patients is Mayzent (siponimod) not recommended?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Patients with concomitant treatment with class Ia or class III anti-arrhythmic medications	146	40	16	20	48	3	3	16
	66%	57%	64%	67%	74%	60%	60%	80%
Patients with QTC prolongation >500 msec	149	41	16	21	48	4	3	16
	68%	59%	64%	70%	74%	80%	60%	80%
Patients with history of recurrent syncope	80	19	5	13	31	2	2	8
	36%	27%	20%	43%	48%	40%	40%	40%
Patients with history of symptomatic bradycardia	150	42	17	25	44	2	4	16
	68%	60%	68%	83%	68%	40%	80%	80%
Patients with uncontrolled hypertension	111	29	14	22	29	3	3	11
	50%	41%	56%	73%	45%	60%	60%	55%
Patients with severe untreated sleep apnoea	59	13	5	19	15	2	1	4
	27%	19%	20%	63%	23%	40%	20%	20%
Patients with active malignancies	147	83	21	25	39	4	3	18
	67%	66%	84%	83%	60%	80%	60%	90%
Patients with controlled hypertension	15	6	2	0	7	1	0	1
	7%	5%	8%	0%	11%	20%	0%	5%
Patients treated with benzodiazepines	16	6	0	0	8	0	0	2
	7%	5%	0%	0%	12%	0%	0%	10%
Patients treated with beta-blockers	71	31	8	6	28	3	2	7
	32%	25%	32%	20%	43%	60%	40%	35%
None of these	2	0	2	0	0	0	0	0
	1%	0%	8%	0%	0%	0%	0%	0%
I don't know/ I am not sure	13	9	0	1	4	0	0	0
	6%	7%	0%	3%	6%	0%	0%	0%
	21	*5*	*1*	*3*	*9*	*0*	*0*	*3*

All correct responses (with or without incorrect responses)	*10%*	*7%*	*4%*	*10%*	*14%*	*0%*	*0%*	*14%*

Green cells indicate correct responses.

Table 10-16 shows that for H-Q17 (duration of monitoring for patients with cardiac conditions) 55% of HCPs selected a response of six hours, aligned with the educational materials, with a further 10% expecting to monitor patients for a longer period of eight hours, reflecting a more conservative clinical approach.

Table 10-16 Detailed response to H-Q17 – How many hours should a patient with sinus bradycardia, 1st /2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
3 Hours	22	8	2	1	10	0	0	1
	10%	11%	8%	3%	15%	0%	0%	5%
5 Hours	18	8	1	2	7	0	0	0
	8%	11%	4%	7%	11%	0%	0%	0%
6 Hours	120	36	18	22	26	3	2	13
	55%	51%	72%	73%	40%	60%	40%	65%
8 Hours	23	4	0	3	10	1	2	3
	10%	6%	0%	10%	15%	20%	40%	15%
I don't know/ I am not sure	37	14	4	2	12	1	1	3
	17%	20%	16%	7%	18%	20%	20%	15%
At least 6 hours of monitoring	*143*	*40*	*18*	*25*	*36*	*4*	*4*	*16*
	65%	*57%*	*72%*	*83%*	*55%*	*80%*	*80%*	*80%*

Green cells indicate correct response.

Table 10-17 shows responses for H-Q18 (ECG findings that would warrant additional monitoring). There were two correct answers to this question: 'New onset second degree or higher AV block' was selected by 71% of HCPs and 'QTc>500 msec" was selected by 60% HCPs, with 55% selecting both. One of the incorrect answer options was selected by just under half of respondents (Transient sinus bradycardia of 50 bmp, 48%), reflecting a more conservative clinical approach that does not pose a risk to patient safety.

Table 10-17 Detailed response to H-Q18 – 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?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**

Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
New onset second degree or higher AV block	156	43	19	20	49	4	4	17
	71%	61%	76%	67%	75%	80%	80%	85%
QTc>500 msec	131	37	19	17	42	3	3	10
	60%	53%	76%	57%	65%	60%	60%	50%
Hypotension	57	27	3	4	17	0	0	6
	26%	39%	12%	13%	26%	0%	0%	30%
Transient sinus bradycardia of 50 bpm	106	40	17	10	31	0	2	6
	48%	57%	68%	33%	48%	0%	40%	30%
None of these	7	3	0	2	2	0	0	0
	3%	4%	0%	7%	3%	0%	0%	0%
I don't know/ I am not sure	24	10	2	4	5	1	0	2
	11%	14%	8%	13%	8%	20%	0%	10%
Both correct responses & no incorrect responses	*37*	*3*	*4*	*8*	*14*	*3*	*3*	*2*
	17%	*4%*	*16%*	*27%*	*22%*	*60%*	*60%*	*10%*
Both correct responses (with or without other responses)	*121*	*33*	*16*	*16*	*40*	*3*	*3*	*10*
	55%	*47%*	*64%*	*53%*	*62%*	*60%*	*60%*	*50%*

Green cells indicate correct responses.

Table 10-18 shows responses for H-Q19 (whether center performs first dose monitoring for patients with CV risk). There were two correct answers to this question and HCPs could select either to be considered correct.

Table 10-18 Detailed response to H-Q19 – Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other specialized MS center for FDM?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Perform first dose monitoring in my own center	160	53	19	28	47	5	4	4
	73%	76%	76%	93%	72%	100%	80%	20%
Send patients to other specialized	51	15	3	2	15	0	1	15
	23%	21%	12%	7%	23%	0%	20%	75%

center for first dose monitoring								
Do not conduct first dose monitoring in patients with CV risk	9 4%	2 3%	3 12%	0 0%	3 5%	0 0%	0 0%	1 5%
Either correct response	*211* *96%*	*19* *95%*	*62* *95%*	*30* *100%*	*68* *97%*	*22* *88%*	*5* *100%*	*5* *100%*

Green cells indicate correct responses.

10.4.6 Titration (HCP)

Figure 7 shows HCP responses to each question pertaining to the assessment of treatment dosing schedule. The responses showed nearly all HCPs answered correctly with regards to 'counselling patients on daily dose'. The remaining responses varied, ranging between 16% and 65% of HCPs selecting the correct response.

Figure 7. Titration – HCP responses

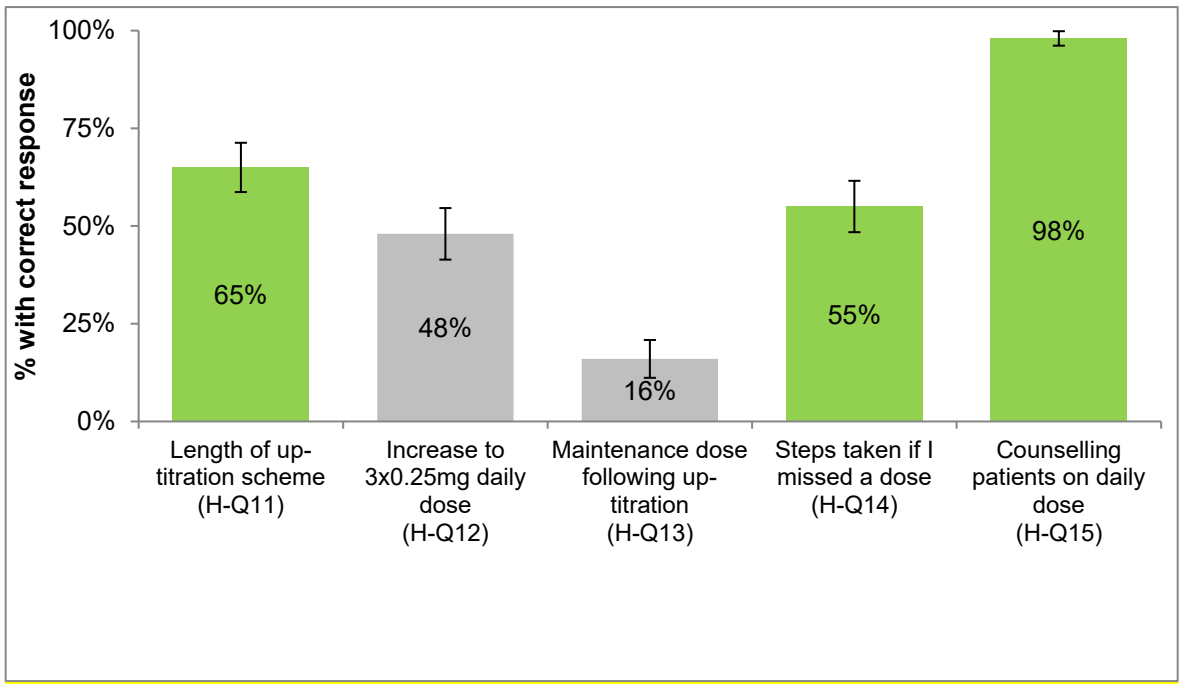


Table 10-19 shows responses for H-Q11 (length of up-titration scheme). There was one correct answer to this question (up-titration scheme takes 5 days to complete), and 27% of HCPs selected this response. Over a third of HCPs (38%) believe the up-titration scheme takes six days. It should be noted that the target dose is only reached on day six, with the day six dose being higher than day five. Therefore, HCPs selecting '6 days' are also considered to have responded correctly.

Table 10-19 Detailed response to H-Q11 – An up-titration scheme is required for Mayzent (siponimod). Please indicate the number of days this scheme takes to complete.

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
3 Days	6	3	0	0	2	1	0	6
	3%	4%	0%	0%	3%	20%	0%	3%
5 Days	60	22	4	15	12	1	1	5
	27%	31%	16%	50%	18%	20%	20%	25%
6 Days	83	20	14	14	27	1	2	5
	38%	29%	56%	47%	42%	20%	40%	25%
7 Days	41	12	5	0	16	2	1	5
	19%	17%	20%	0%	25%	40%	20%	25%
I don't know/ I am not sure	30	13	2	1	8	0	1	5
	14%	19%	8%	3%	12%	0%	20%	25%
Either 5 days or 6 days	*143*	*42*	*18*	*29*	*39*	*2*	*3*	*10*
	65%	*60%*	*72%*	*97%*	*60%*	*40%*	*60%*	*50%*

Green cells indicate correct response.

Table 10-20 shows that responses for H-Q12 (timing of dose increase to 3x0.25mg) were varied, with just under half of HCPs (48%) correctly identifying that day four is when patients increase their dose in the up-titration schedule, and other responses ranging from day one to day 14. 25% of HCPs were not sure which day the increase to 3 x 0.25mg should occur. Information on the daily dose is included within the titration pack.

Table 10-20 Detailed response to H-Q12 – When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Day 1	2	0	0	0	2	0	0	0
	1%	0%	0%	0%	3%	0%	0%	0%
Day 2	1	0	0	0	1	0	0	0
	0%	0%	0%	0%	2%	0%	0%	0%
Day 3	29	11	1	6	6	2	1	2
	13%	16%	4%	20%	9%	40%	20%	10%
Day 4	106	26	19	20	26	3	3	9

	48%	37%	76%	67%	40%	60%	60%	45%
Day 5	9	5	0	2	1	0	0	1
	4%	7%	0%	7%	2%	0%	0%	5%
Day 6	4	0	1	1	2	0	0	0
	2%	0%	4%	3%	3%	0%	0%	0%
Day 7	8	2	0	1	4	0	0	1
	4%	3%	0%	3%	6%	0%	0%	5%
Day 8	2	0	1	0	1	0	0	0
	1%	0%	4%	0%	2%	0%	0%	0%
Day 10	1	0	0	0	1	0	0	0
	0%	0%	0%	0%	2%	0%	0%	0%
Day 14	4	2	0	0	2	0	0	0
	2%	3%	0%	0%	3%	0%	0%	0%
I don't know/ I am not sure	54	24	3	0	19	0	1	7
	25%	34%	12%	0%	29%	0%	20%	35%

Green cells indicate correct response.

Table 10-21 shows responses for H-Q13, the recommended maintenance doses following up-titration. There were two correct answers to this question (1 mg & 2mg), which were selected by 27% and 71% of HCPs respectively. Whilst only small numbers of HCPs selected any of the incorrect responses, there were only 16% of HCPs who selected both correct answers. 2mg is the maintenance dose for most patients, with 1mg only used in specific patient types. The question did not specify any particular genotype.

Table 10-21 Detailed response to H-Q13 – The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are:

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
0.5 mg	2	0	0	0	2	0	0	0
	1%	0%	0%	0%	3%	0%	0%	0%
1 mg	60	17	6	19	9	2	1	0
	27%	24%	24%	63%	14%	40%	20%	0%
1.25 mg	17	8	0	1	7	0	0	1
	8%	11%	0%	3%	11%	0%	0%	5%
2 mg	156	42	22	27	41	4	4	16

	71%	60%	88%	90%	63%	80%	80	80%
I don't know/ I am not sure	20 9%	7 10%	3 12%	0 0%	7 11%	0 0%	1 20%	2 10%
All correct responses & no incorrect responses	*35* *16%*	*4* *6%*	*6* *24%*	*17* *57%*	*1* *2%*	*1* *20%*	*1* *20%*	*5* *25%*

Green cells indicate correct responses.

Table 10-22 shows responses for H-Q14 (actions if dose missed for more than one day during up-titration scheme). There was only one correct answer to this question (the titration schedule needs to be restarted with a new titration pack), which was selected by 55% of HCPs. 20% of HCPs believed that no additional steps were required, and titration should continue with the missing dose taken the next day.

Table 10-22 Detailed response to H-Q14 – What steps need to be taken if a dose is missed for more than one day during the first 6 days treatment initiation?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220** ***100%***	**70** ***100%***	**25** ***100%***	**30** ***100%***	**65** ***100%***	**5** ***100%***	**5** ***100%***	**20** ***100%***
The titration schedule needs to be restarted with a new titration pack	120 55%	30 43%	16 64%	24 80%	34 52%	3 60%	3 60	10 50%
The titration schedule needs to be re-started only if this is within the first 4 days of treatment	29 13%	11 16%	0 0%	2 7%	13 20%	0 0%	1 20%	2 10%
None, the titration is to be continued with the missing dose taken the next day	44 20%	18 26%	8 32%	5 17%	9 14%	1 20%	0 0%	3 15%
The patient shall not be further treated with Mayzent (siponimod)	7 3%	4 6%	1 4%	0 0%	2 3%	0 0%	0 0%	0 0%
I don't know/ I am not sure	25 11%	11 16%	0 0%	0 0%	7 11%	1 20%	1 20%	5 25%

Green cells indicate correct response.

Table 10-23 Detailed response to H-Q15 – Have you counselled your patients on the importance of taking their daily dose of Mayzent (siponimod), during both titration and maintenance phases of treatment?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**

Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	215	67	25	30	65	5	4	19
	98%	96%	100%	100%	100%	100%	80%	95%
No	5	3	0	0	0	0	1	5
	2%	4%	0%	0%	0%	0%	20%	2%

Green cells indicate correct response.

10.4.7 During treatment (HCP)

Figure 8 shows HCP responses to each question pertaining to assessment of steps in ophthalmology checklist, managing infection risk, liver function and skin examination. The responses showed varying levels of understanding with five questions achieving over 70% and two achieving 50-69% correct responses. The remaining two questions were answered correctly by less than 50% of HCPs.

Figure 8. During treatment – HCP responses

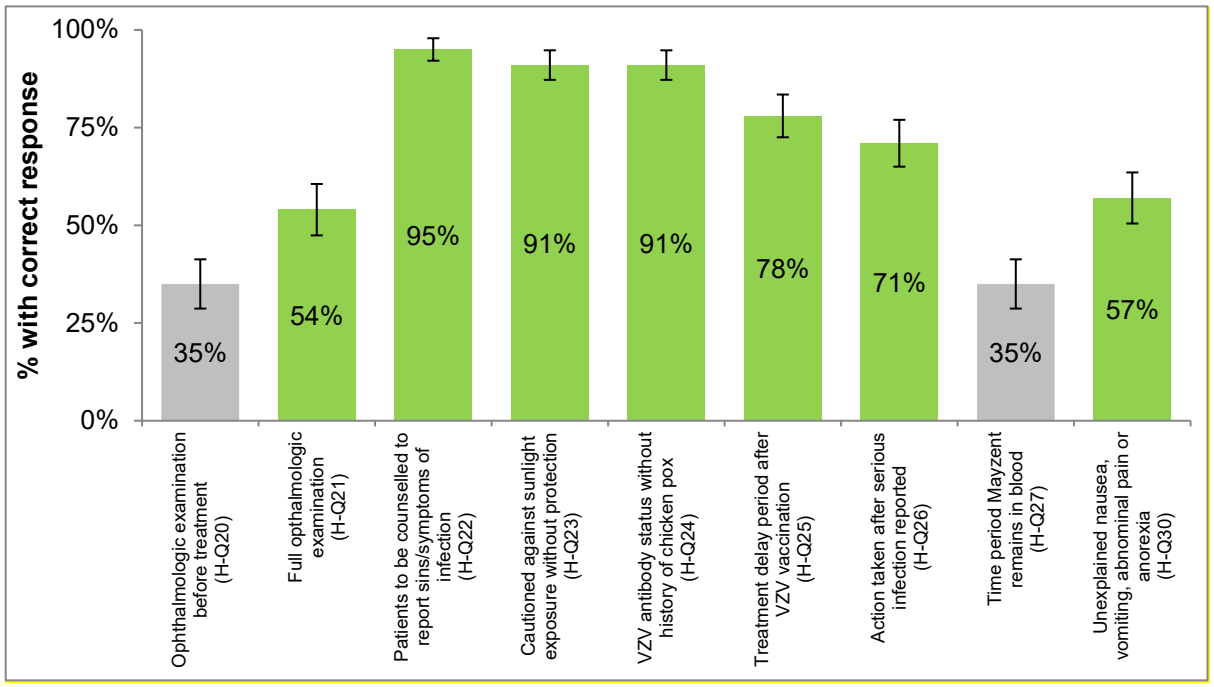


Table 10-24 shows responses for H-Q20, relating to requirements for ophthalmologic examinations. There were three correct answers to this question (Diabetes mellitus, Uveitis and History of retinal disorders), which were selected by 60%, 55% and 59% of HCPs respectively, with 35% of HCPs selecting all three. 29% of HCPs selected they would conduct ophthalmologic examination in patients with 'severe myopia' - this is not required for Mayzent initiation but may reflect a more conservative approach in clinical practice.

Table 10-24 Detailed response to H-Q20 – For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Diabetes mellitus	133	37	15	18	38	4	4	17
	60%	53%	60%	60%	58%	80%	80%	85%
Uveitis	120	36	17	19	34	2	4	8
	55%	51%	68%	63%	52%	40%	80%	40%
History of retinal disorders	129	44	3	20	42	3	4	13
	59%	63%	12%	67%	65%	60%	80%	65%
Severe Myopia	64	27	5	5	22	0	0	5
	29%	39%	20%	17%	34%	0%	0%	25%
None of these	6	2	2	1	1	0	0	0
	3%	3%	8%	3%	2%	0%	0%	0%
I don't know/I am not sure	29	11	3	5	8	1	1	0
	13%	16%	12%	17%	12%	20%	20%	0%
All correct responses & no incorrect responses	*38*	*6*	*0*	*12*	*12*	*2*	*4*	*2*
	17%	*9%*	*0%*	*40%*	*18%*	*40%*	*80%*	*10%*
All correct responses (with or without incorrect responses)	*78*	*24*	*1*	*16*	*26*	*2*	*4*	*5*
	35%	*34%*	*4%*	*53%*	*40%*	*40%*	*80%*	*25%*

Green cells indicate correct responses.

Table 10-25 shows responses for H-Q21 (timing of ophthalmologic examination). Over half (54%) of HCPs selected the correct answer of 3-4 months following initiation to conduct a full ophthalmologic evaluation. 15% of HCPs expect to conduct the evaluation earlier (1-2 months), and only a minority expect to wait longer than 12 months.

Table 10-25 Detailed response to H-Q21 – At what time after starting treatment should a full ophthalmologic evaluation be performed?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
1-2 months	32	12	5	4	7	1	0	3
	15%	17%	20%	13%	11%	20%	0%	15%
3-4 months	118	32	16	22	26	3	4	15

	54%	46%	64%	73%	40%	60%	80%	75%
5-12 months	46	15	3	3	23	0	1	46
	21%	21%	12%	10%	35%	0%	20%	21%
13-24 months	4	2	0	0	2	0	0	4
	2%	3%	0%	0%	3%	0%	0%	2%
I don't know/ I am not sure	20	9	1	1	7	1	0	20
	9%	13%	4%	3%	11%	20%	0%	9%

Green cells indicate correct response.

Table 10-26 Detailed response to H-Q22 – Patients receiving Mayzent (siponimod) should be counselled to report signs and symptoms of infection immediately to their prescriber

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	210	64	25	29	64	5	4	19
	95%	91%	100%	97%	98%	100%	80%	95%
No	8	4	0	1	1	0	1	8
	4%	6%	0%	3%	2%	0%	20%	4%
I don't know/ I am not sure	2	2	0	0	0	0	0	0
	1%	3%	0%	0%	0%	0%	0%	0%

Green cells indicate correct response.

Table 10-27 Detailed response to H-Q23 – Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	200	59	23	29	61	4	5	19
	91%	84%	92%	97%	94%	80%	100%	95%
No	7	3	0	0	3	1	0	0
	3%	4%	0%	0%	5%	20%	0%	0%
I don't know/ I am not sure	13	8	2	1	1	0	0	1
	6%	11%	8%	3%	2%	0%	0%	5%

Green cells indicate correct response.

Table 10-28 Detailed response to H-Q24 – You should check varicella zoster virus antibody status in patients receiving Mayzent (siponimod) without a healthcare professionally confirmed history of chicken pox

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	201	60	24	28	60	4	5	20
	91%	86%	96%	93%	92%	80%	100%	100%
No	2	0	0	1	1	0	0	0
	1%	0%	0%	3%	2%	0%	0%	0%
I don't know/ I am not sure	17	10	1	1	4	1	0	0
	8%	14%	4%	3%	6%	20%	0%	0%

Green cells indicate correct response.

Table 10-29 shows responses for H-Q25 (length of treatment delay after VZV vaccination). There was only one correct answer to this question (one month), which was selected by over half of respondents (52%), with a further 26% expecting a longer treatment delay. Responses of at least 1 month are considered clinically meaningful and pose no risk to patients.

Table 10-29 Detailed response to H-Q25 – Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
2 weeks	11	3	3	2	1	0	0	2
	5%	4%	12%	7%	2%	0%	0%	10%
1 month	115	30	17	21	29	4	3	11
	52%	43%	68%	70%	45%	80%	60%	55%
2 months	19	3	1	2	7	1	1	4
	9%	4%	4%	7%	11%	20%	20%	20%
3 months	37	15	1	2	15	0	1	3
	17%	21%	4%	7%	23%	0%	20%	15%
I don't know/ I am not sure	38	19	3	3	13	0	0	0
	17%	27%	12%	10%	20%	0%	0%	0%
At least 1 month	*171*	*48*	*19*	*25*	*51*	*5*	*5*	*18*

	78%	*69%*	*76%*	*83%*	*78%*	*100%*	*100%*	*90%*

Green cells indicate response.

Table 10-30 Detailed response to H-Q26 – What action should be taken if a patient reports serious infection during treatment on Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Perform prompt diagnostic evaluation and initiate appropriate treatment if diagnosed	27	3	3	2	8	0	2	4
	12%	4%	12%	7%	12%	0%	40%	20%
Consider treatment suspension if there are signs and symptoms that may be suggestive of progressive leukoencephalopathy (PML) or cryptococcal meningitis (CM)	34	30	17	21	8	0	2	1
	15%	43%	68%	70%	12%	0%	40%	5%
Both of the above	157	3	1	2	41	4	1	15
	71%	4%	4%	7%	63%	80%	20%	75%
I don't know/ I am not sure	2	15	1	2	0	0	0	0
	1%	21%	4%	7%	0%	0%	0%	0%

Green cells indicate correct response.

Table 10-31 shows responses for H-Q27 (length of time siponimod remains in the blood after treatment ends). There was only one correct answer to this question (10 days), which was selected by 35% of HCPs. Almost 1/3 of HCPs selected 'I don't know/I am not sure' (32%).

Table 10-31 Detailed response to H-Q27 – After stopping treatment, for how long does Mayzent (siponimod) remain in the blood?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
5 day	22	6	4	2	6	0	1	3
	10%	9%	16%	7%	9%	0%	20%	15%
10 days	76	17	13	17	15	1	2	11
	35%	24%	52%	57%	23%	20%	40%	55%
15 days	27	6	1	1	18	0	0	1

	12%	9%	4%	3%	28%	0%	0%	5%
20 days	25	13	3	2	4	0	1	2
	11%	19%	12%	7%	6%	0%	20%	10%
I don't know/ I am not sure	70	28	4	8	22	4	1	3
	32%	40%	16%	27%	34%	80%	20%	15%

Green cells indicate correct response.

Table 10-32 shows responses for H-Q30, the actions required if a patient shows signs of liver impairment. There were two correct answers for this question (Check liver enzymes & Discontinue treatment if significant liver injury is confirmed), which were selected by 79% and 74% of HCPs respectively. 57% correctly selected both options and did not select any incorrect options.

Table 10-32 Detailed response to H-Q30 – What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Continue as nothing serious could happen	15	8	1	0	6	0	0	0
	7%	11%	4%	0%	9%	0%	0%	0%
Check liver enzymes	174	55	20	25	46	3	5	20
	79%	79%	80%	83%	71%	60%	100%	100%
Discontinue treatment if significant liver injury is confirmed	162	48	19	26	44	5	4	16
	74%	69%	76%	87%	68%	100%	80%	80%
I don't know/ I am not sure	5	3	0	0	2	0	0	0
	2%	4%	0%	0%	3%	0%	0%	0%
Both correct responses & no incorrect responses	*125*	*40*	*13*	*21*	*28*	*3*	*4*	*16*
	57%	*57%*	*52%*	*70%*	*43%*	*60%*	*80%*	*80%*

Green cells indicate correct responses.

10.4.8 Risk of pregnancy (HCP)

Figure 9 shows HCP responses to each question pertaining to the risk of pregnancy in patients receiving Mayzent.

Figure 9. Risk of pregnancy – HCP responses

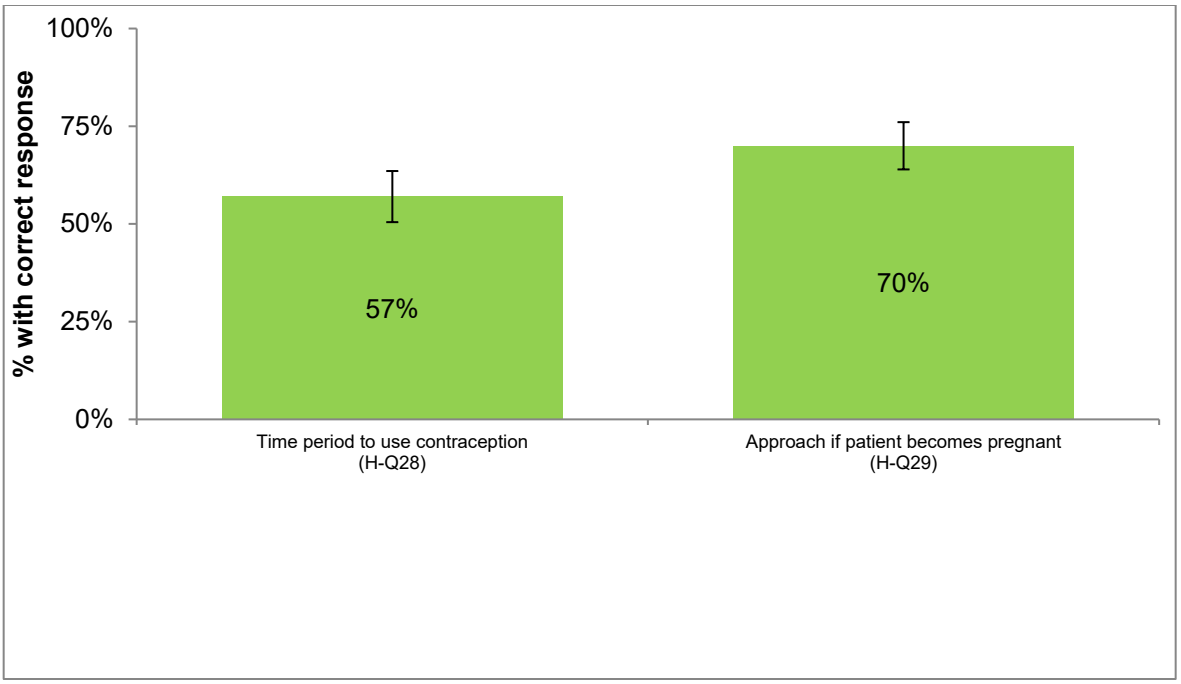


Table 10-33 shows responses for H-Q28 (how long a female patient should use effective contraception after siponimod is discontinued). There was one correct answer aligned with the educational materials (10 days), which was selected by 40% of HCPs, with 57% selecting a response of 10 days or more. A similar number of HCPs selected 'don't know' (39%), with only a small number of HCPs selecting shorter time periods.

Table 10-33 Detailed response to H-Q28 – Day - For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod) ? For at least… days

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
2	1	0	0	0	1	0	0	0
	0%	0%	0%	0%	2%	0%	0%	0%
3	1	1	0	0	0	0	0	0
	0%	1%	0%	0%	0%	0%	0%	0%
5	1	1	0	0	0	0	0	0
	0%	1%	0%	0%	0%	0%	0%	0%
7	7	1	1	0	4	0	0	1
	3%	1%	4%	0%	6%	0%	0%	5%
10	89	21	17	17	19	3	1	11
	40%	30%	68%	57%	29%	60%	20%	55%

14	2	1	0	1	0	0	0	0
	1%	1%	0%	3%	0%	0%	0%	0%
15	2	0	0	0	2	0	0	0
	1%	0%	0%	0%	3%	0%	0%	0%
20	2	1	0	1	0	0	0	0
	1%	1%	0%	3%	0%	0%	0%	0%
21	1	1	0	0	0	0	0	0
	0%	1%	0%	0%	0%	0%	0%	0%
28	4	1	0	0	3	0	0	0
	2%	1%	0%	0%	5%	0%	0%	0%
30	25	5	1	3	10	1	2	3
	11%	7%	4%	10%	15%	20%	40%	15%
I don't know/ I am not sure	85	37	6	8	26	1	2	5
	39%	53%	24%	27%	40%	20%	40%	25%
At least 10 days	*125*	*30*	*18*	*22*	*34*	*4*	*3*	*14*
	57%	*43%*	*72%*	*73%*	*52%*	*80%*	*60%*	*70%*

Green cells indicate correct response.

Table 10-34 shows responses for H-Q29 (actions required if a patient becomes pregnant while on siponimod). There were two correct answers listed in the protocol (patient treatment should be discontinued immediately & pregnancy should be reported to Novartis), which were selected by 70% and 36% of HCPs respectively. Reporting the pregnancy to Novartis is not a mandatory step and therefore, from a clinical perspective, those selecting the first response (discontinue treatment immediately) are considered to have responded correctly.

Table 10-34 Detailed response to H-Q29 – For patients who become pregnant during treatment, what is the correct approach from the options below?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**220**	**70**	**25**	**30**	**65**	**5**	**5**	**20**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Patient treatment should be discontinued immediately	154	48	21	22	35	5	5	18
	70%	69%	84%	73%	54%	100%	100%	90%
Patient should be titrated off treatment	38	15	1	2	19	0	0	1
	17%	21%	4%	7%	29%	0%	0%	5%
Pregnancy should be reported to Novartis	79	20	10	15	15	3	2	14
	36%	29%	40%	50%	23%	60%	40%	70%
None of these	6	2	0	1	3	0	0	0
	3%	3%	0%	3%	5%	0%	0%	0%

I don't know/ I am not sure	22	8	2	1	10	0	0	1
	10%	11%	8%	3%	15%	0%	0%	5%

Green cells indicate correct responses.

10.4.9 Receipt of materials (Patient/Caregiver)

Figure 10 shows patients' responses to the question pertaining to educational materials being received. The responses showed that just over 50% of patients/carers recall receiving any educational material for Mayzent (siponimod). It is unknown when patients were initiated on Mayzent and may have received the educational materials, or how much time has elapsed prior to them completing the survey.

Figure 10. Assessment of education material received – patient caregiver responses

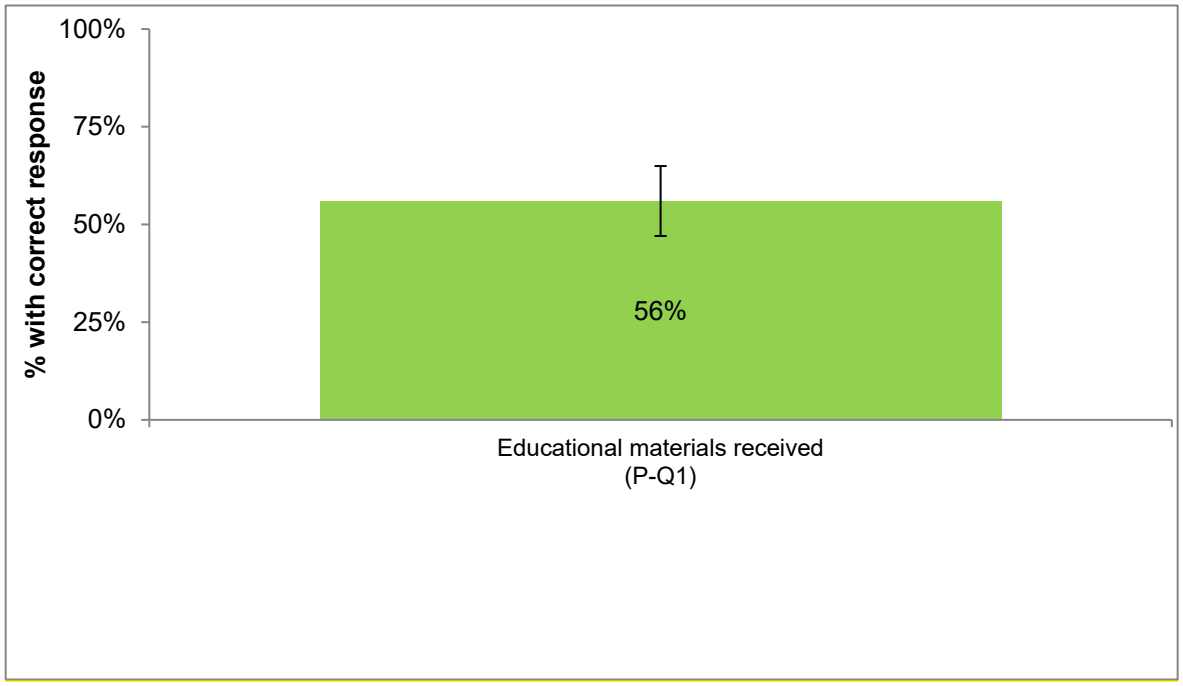


Table 10-35 Detailed response to P-Q1 – Have you / the person you are caring for with SPMS received any education materials for Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	66	31	6	4	13	3	5	4
	56%	89%	33%	27%	37%	60%	100%	80%
No	33	3	6	7	17	0	0	0
	28%	9%	33%	47%	49%	0%	0%	0%

I don't know/ I am not sure	19	1	6	4	5	2	0	0
	16%	3%	33%	27%	14%	40%	0%	1%

10.4.10 Patient identification and eligibility (Patient/Caregiver)

Figure 11 shows patient/caregiver responses to each question pertaining to assessment of knowledge of testing before initiation or treatment. Only one of the five questions was correctly answered by over 70% of patients/caregivers which related to the requirement for an ECG. The remaining responses showed low awareness of the requirements prior to initiation of Mayzent. Three questions with low correct responses required selection of multiple correct responses to be considered fully correct.

Figure 11. Patient identification and eligibility – patient caregiver responses

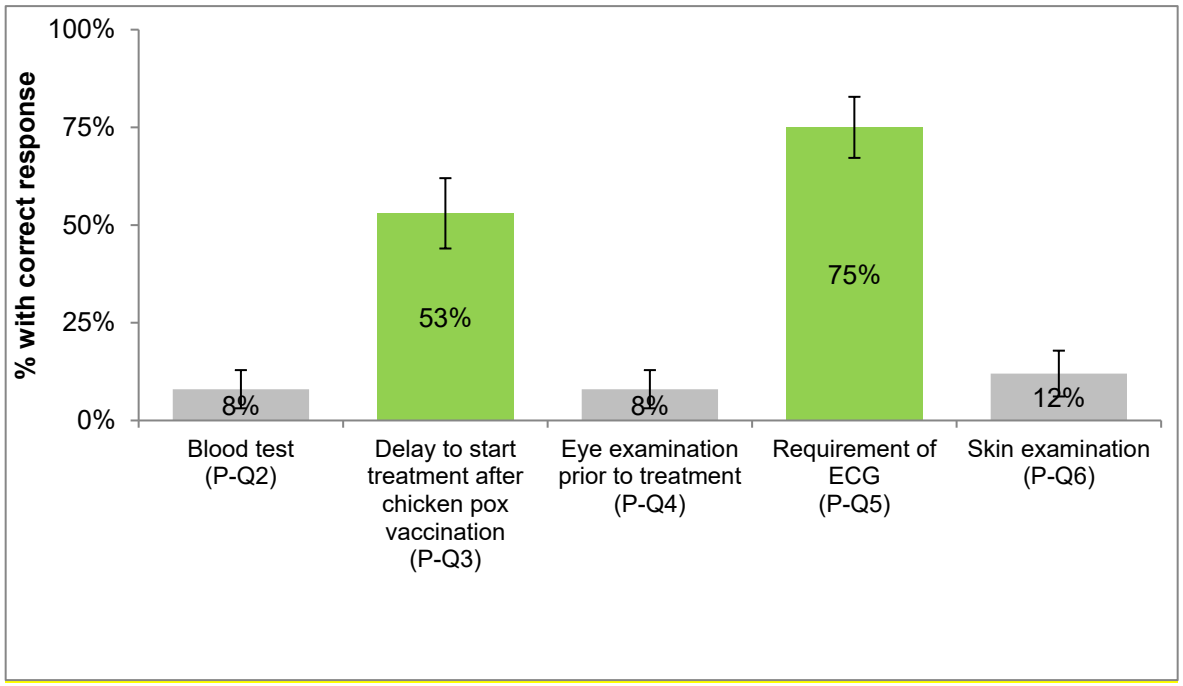


Table 10-36 shows responses for P-Q2 (blood tests required prior to initiation). There were three correct answers included in the protocol (CYP2C9 genotype, white blood cell count & liver function), which were selected by 39%, 36% and 47% of patients/caregivers respectively. However, the educational materials state "your blood may also be tested to check your blood cell count…" and so Hematocrit has also been considered a correct response. This was selected by 21% of patients/caregivers, resulting in 8% selecting all four correct responses. 78% of patients/caregivers selected at least one of the correct responses.

Table 10-36 Detailed response to P-Q2 – For what reasons will the doctor do a blood test before you get ready for your treatment with Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**

	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
CYP2C9 genotype (a gene that can modify how fast or slow siponimod can be transformed within your body)	46 39%	21 60%	10 56%	1 14%	10 29%	0 0%	3 60%	1 20%
White blood cell count	43 36%	12 34%	12 67%	2 29%	7 20%	1 20%	4 80%	3 60%
Liver function	55 47%	22 63%	8 44%	2 29%	10 29%	3 60%	3 60%	4 80%
Hepatitis Type B	18 15%	7 20%	2 11%	1 14%	5 14%	0 0%	1 20%	2 40%
Hematocrit (concentration of red cells in your blood)	25 21%	10 29%	3 17%	2 29%	7 20%	0 0%	0 0%	2 40%
None of these	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
I don't know/ I am not sure	24 20%	1 3%	1 6%	4 57%	0 0%	1 20%	0 0%	1 20%
At least one correct response	*92* *78%*	*34* *97%*	*17* *94%*	*7* *47%*	*21* *60%*	*4* *80%*	*5* *100%*	*4* *80%*
All correct responses (with or without other responses)	*10* *8%*	*7* *20%*	*1* *6%*	*0* *0%*	*1* *3%*	*0* *0%*	*0* *0%*	*1* *20%*

Green cells indicate correct responses.

Table 10-37 shows responses for P-Q3 (treatment delay following chicken pox vaccination). There was only one correct answer to this question (1 month), which was selected by 21% of patients/caregivers, with a further 32% selecting a longer time period which would not pose a risk to patient safety. However, a high proportion of patients/caregivers selected 'I don't know/I am not sure' (47%).

Table 10-37 Detailed response to P-Q3 – 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)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
6 months	14 12%	0 0%	1 6%	2 13%	7 20%	1 20%	0 0%	0 0%
4 months	5	0	1	0	3	1	0	0

	4%	0%	6%	0%	9%	20%	0%	0%
2 months	18	5	7	0	3	0	3	0
	15%	14%	39%	0%	9%	0%	60%	0%
1 month	25	13	5	2	3	0	2	0
	21%	37%	28%	13%	9%	0%	40%	0%
I don't know/ I am not sure	56	14	4	11	19	3	0	5
	47%	40%	22%	73%	54%	60%	0%	100%
At least 1 month	*62*	*21*	*14*	*4*	*16*	*2*	*5*	*0*
	53%	*60%*	*78%*	*27%*	*46%*	*40%*	*100%*	*0%*

Green cells indicate correct response.

Table 10-38 shows responses for P-Q4 (reasons for ophthalmologic examination). There were three correct answers to this question, which were selected by 47%, 26% and 19% of patients/caregivers respectively, with 8% selecting all three correct answers. 57% selected at least one correct answer.

Table 10-38 Detailed response to P-Q4 – For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with Mayzent (siponimod)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Have or have had previously visual disturbances or vision problems in the center of the eye	56	18	10	6	13	5	4	0
	47%	51%	56%	40%	37%	100%	80%	0%
Have or have had previously inflammation of the eye	31	15	8	0	7	0	0	1
	26%	43%	44%	0%	20%	0%	0%	20%
Have or have had previously high blood sugar levels/Diabetes	22	5	8	1	4	1	3	0
	19%	14%	44%	7%	11%	20%	60%	0%
Cataract (when the lens of your eye becomes opaque or loses its transparency)	19	6	5	0	8	0	0	0
	16%	17%	28%	0%	23%	0%	0%	%
Hypertension status	25	10	1	0	9	1	4	0
	21%	29%	6%	0%	26%	20%	80%	%
None of these	10	4	3	0	1	0	0	2
	8%	11%	17%	0%	3%	0%	0%	40%
I don't know/ I am not sure	31	6	1	9	13	0	0	2
	26%	17%	6%	60%	37%	0%	0%	40%

All correct responses (with or without other responses)	*9*	*2*	*4*	*0*	*3*	*0*	*0*	*0*
	8%	*6%*	*22%*	*0%*	*9%*	*0%*	*0%*	*0%*
1 or more correct response	*67*	*23*	*13*	*6*	*15*	*5*	*4*	*1*
	57%	*66%*	*72%*	*40%*	*43%*	*100%*	*80%*	*20%*

Green cells indicate correct responses.

Table 10-39 Detailed response to P-Q5 – 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)

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	88	32	14	12	20	3	5	2
	75%	91%	78%	80%	57%	60%	100%	40%
No	9	2	1	0	3	1	0	2
	8%	6%	6%	0%	9%	20%	0%	40%
I don't know/ I am not sure	21	1	3	3	12	1	0	1
	18%	3%	17%	20%	34%	20%	0%	20%

Green cells indicate correct response.

Table 10-40 shows responses for P-Q6 (need for skin examinations). There were two correct answers to this question, both of which were selected by less than 50% of patients/caregivers, and only 12% selected both the correct responses. 69% of patients/caregivers selected at least one of the correct responses, indicating awareness of the need for skin examinations, albeit with lower knowledge of the appropriate timing of these.

Table 10-40 Detailed response to P-Q6 – When, if at all, may the doctor want to conduct a skin examination?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Prior to treatment initiation	39	16	2	4	11	2	4	0
	33%	46%	11%	27%	31%	40%	80%	0%
Every 6-12 months following initiation	56	24	7	4	13	4	1	0
	47%	69%	39%	47%	37%	80%	20%	0%

Not at all	7	0	1	0	2	0	0	4
	6%	0%	6%	0%	6%	0%	0%	80%
I don't know/ I am not sure	30	2	8	6	12	1	0	1
	25%	6%	44%	4%	34%	20%	0%	20%
At least 1 correct response	*81*	*33*	*9*	*9*	*21*	*4*	*5*	*0*
	69%	*94%*	*50%*	*60%*	*60%*	*80%*	*100%*	*0%*
Both correct responses	*14*	*7*	*0*	*2*	*3*	*2*	*0*	*0*
	12%	*20%*	*0%*	*13%*	*9%*	*40%*	*0%*	*0%*

Green cells indicate correct responses.

10.4.11 Initiation and first dose / Titration (Patient/Caregiver)

Figure 12 shows patients responses to each question pertaining to the assessment of knowledge for treatment initiation and titration. The responses showed varying levels of understanding with only one question achieving over 70% correct responses relating to the awareness of titration period at start of treatment. With the remaining four responses, two were 50-69% with the other two showing less than 50% correct responses.

Figure 12. Initiation and first dose/ Titration – patient caregiver responses

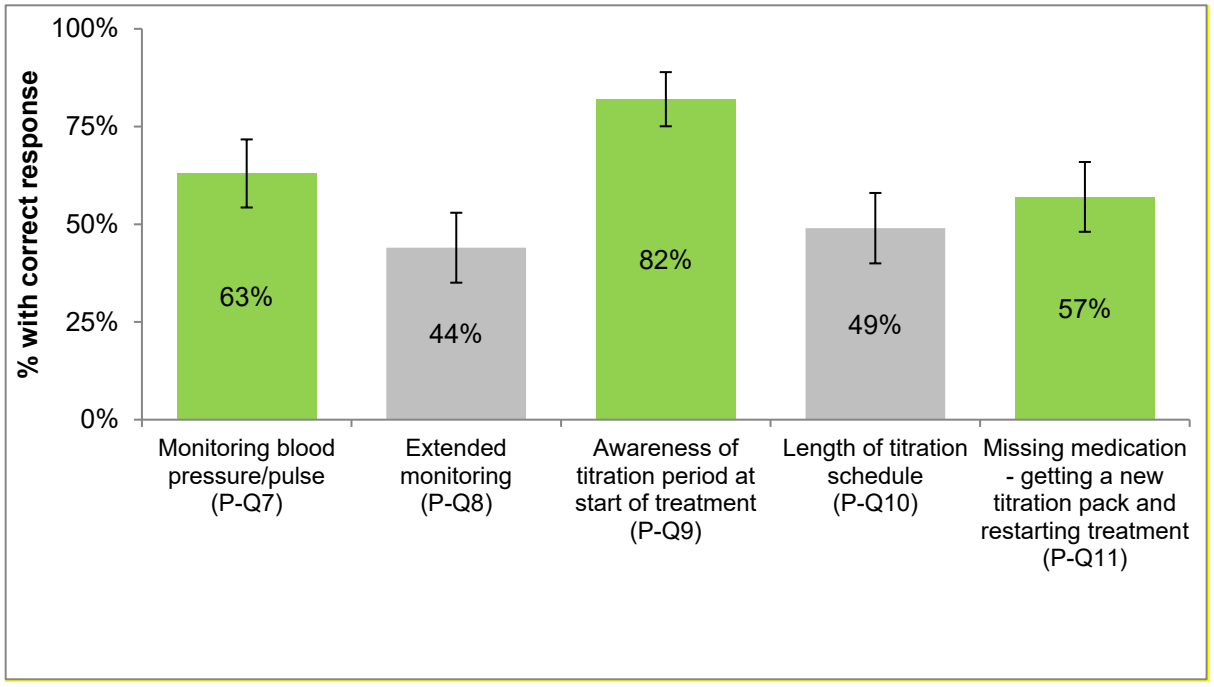


Table 10-41 shows responses for P-Q7 (duration of first dose monitoring). 30% selected 'Not applicable, I don't/the person I care for doesn't have heart problems'. For the remaining patients/caregivers, there was only one correct answer to this question (six hours), which was selected by 52% of patients/caregivers responding, with a further 11% selecting a longer duration (nine hours) which would represent a more conservative clinical practice.

Table 10-41 Detailed response to P-Q7 – At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask you to stay in the clinic after taking the first dose so that your blood pressure and pulse can be monitored?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Not applicable, I don't/ the person I care for doesn't have heart problems	35	7	5	3	16	1	0	1
	30%	20%	28%	20%	46%	20%	0%	20%
Base (excluding n/a)	**83**	**28**	**13**	**12**	**19**	**4**	**5**	**2**
3 hours	17	2	3	6	3	1	2	0
	20%	7%	23%	50%	16%	25%	40%	0%
6 hours	43	20	6	3	10	2	1	1
	52%	71%	46%	25%	53%	50%	20%	50%
9 hours	9	4	3	0	0	0	2	0
	11%	14%	23%	0%	0%	0%	40%	0%
I don't know/ I am not sure	14	2	1	3	6	1	2	1
	17%	7%	8%	25%	32%	25%	0%	50%
At least 6 hours of monitoring	*52*	*24*	*9*	*3*	*10*	*2*	*3*	*1*
	63%	*86%*	*69%*	*25%*	*53%*	*50%*	*60%*	*50%*

Green cells indicate correct response.

Table 10-42 shows responses for P-Q8 (reasons for extended monitoring). There was only one correct answer to this question (Your/Their ECG (electrocardiogram – to check the rhythm of your heart) shows abnormalities), which was selected by 44% of patients/caregivers. In practice, HCPs may use their clinical judgement to continue to monitor patients experiencing anxiety

Table 10-42 Detailed response to P-Q8 – 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?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
You/They experience a feeling of anxiety	17	6	1	1	6	2	1	0
	14%	17%	6%	7%	17%	40%	20%	0%
Your/Their ECG (electrocardiogram – to check the rhythm of your heart) shows abnormalities	52	26	6	5	11	3	0	1
	44%	74%	33%	33%	31%	60%	0%	20%

Your/Their blood pressure goes up	48	12	12	4	11	3	4	2
	41%	34%	67%	27%	31%	60%	80%	40%
Your/Their blood sugar levels increase	13	5	3	3	1	0	1	0
	11%	14%	17%	20%	3%	0%	20%	0%
None of these	13	2	1	2	6	0	0	2
	11%	6%	6%	13%	17%	0%	0%	40%
I don't know/ I am not sure	22	2	3	6	10	0	0	1
	19%	6%	17%	40%	29%	0%	0%	20%

Green cells indicate correct response.

Table 10-43 Detailed response to P-Q9 – Are you aware that there is a period of titration/ up-dosing at the start of treatment with Mayzent (siponimod).

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	97	30	14	9	30	4	5	5
	82%	86%	78%	60%	86%	80%	100%	100%
No	21	5	2	6	5	1	0	0
	18%	14%	22%	40%	14%	20%	0%	0%

Green cells indicate correct response.

Table 10-44 shows responses for P-Q10 (duration of titration schedule). There was only one correct answer to this question according to the protocol (five days), which was selected by 26% of patients/caregivers, with a further 23% selecting '6 days'. Similar to the HCPs, it should be noted that the target dose is only reached on day six with the day six dose being higher than day five. Therefore, patients/caregivers selecting '6 days' are also considered to have responded correctly.

Table 10-44 Detailed response to P-Q10 – For how many days is the titration / up-dosing schedule (pack)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
3 days	15	8	2	1	2	0	0	1
	13%	23%	11%	7%	6%	0%	0%	20%
5 days	31	10	5	4	6	2	2	2
	26%	29%	28%	27%	17%	40%	40%	40%

6 days	27	5	5	4	9	2	2	0
	23%	14%	28%	27%	26%	40%	40%	0%
7 days	20	9	3	1	6	1	1	0
	17%	26%	17%	7%	17%	20%	20%	0%
I don't know/ I am not sure	25	3	9	5	12	0	0	2
	21%	9%	17%	33%	34%	0%	0%	40%
Either 5 days or 6 days	*58*	*15*	*10*	*8*	*15*	*4*	*4*	*2*
	49%	*43%*	*56%*	*53%*	*43%*	*80%*	*80%*	*40%*

Green cells indicate correct response.

Table 10-45 shows responses for P-Q11 (action required if tablet missed during titration period). There was only one correct answer to this question (Yes), which was selected by 57% of patients/caregivers. Of the remaining patients/ caregivers, more selected 'I don't know/I am not sure' (28%) than 'No' (15%).

Table 10-45 Detailed response to P-Q11 – 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

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	67	19	12	6	19	1	5	5
	57%	54%	67%	40%	54%	20%	100%	100%
No	18	8	2	2	6	0	0	0
	15%	23%	11%	13%	17%	0%	0%	0%
I don't know/ I am not sure	33	8	4	7	10	4	0	0
	28%	23%	22%	47%	29%	80%	0%	0%

Green cells indicate correct response.

10.4.12 During treatment (Patient/Caregiver)

Figure 13 shows patient/caregiver responses to each question pertaining to knowledge of side effects and potential risks during treatment. The patient/caregiver survey showed that three questions were answered correctly by more than 70% with one question between 50-69% and the remaining two questions achieving less than 50% correct responses.

Figure 13. During treatment – patient caregiver responses

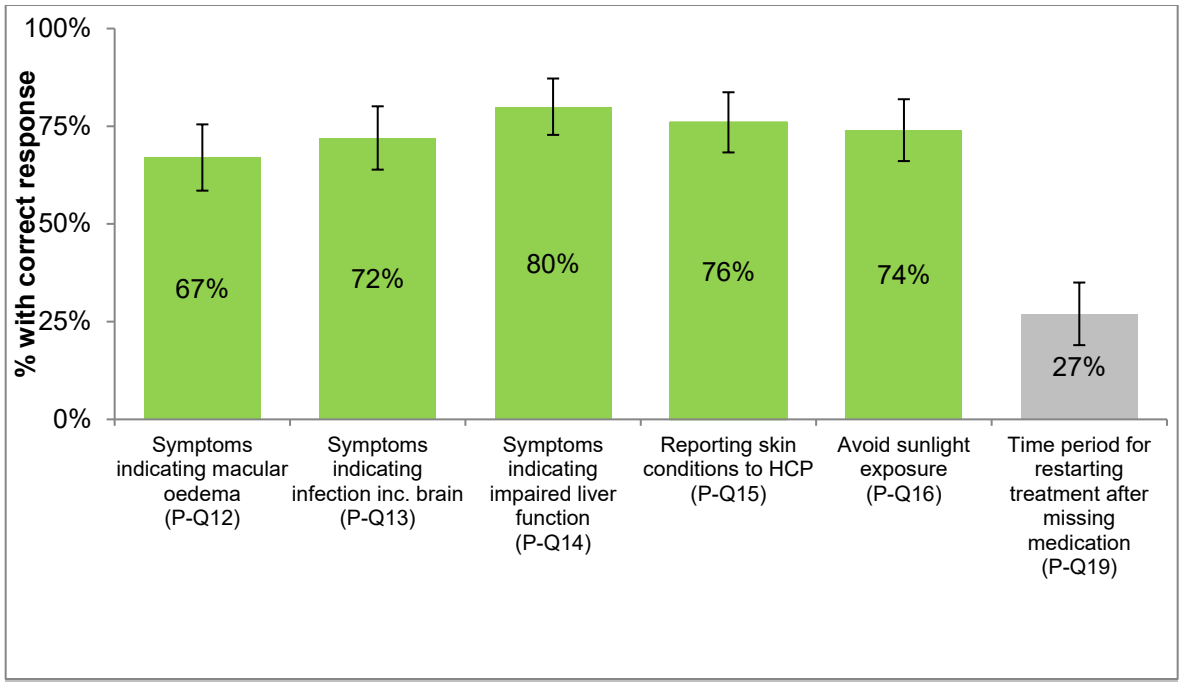


Table 10-46 shows responses for P-Q12 (symptoms indicating macular oedema). There were three correct answers for this question, which were selected by 63%, 21% and 27% of patients/caregivers, with 8% selecting all correct answers. 67% of patients/caregivers selected at least one correct answer.

Table 10-46 Detailed response to P-Q12 – 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)?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Blurred or wavy vision	74	29	15	6	18	1	2	3
	63%	83%	83%	40%	51%	20%	40%	60%
Changes in color / color looking faded	25	11	5	1	5	2	0	1
	21%	31%	28%	7%	14%	40%	0%	20%
Loss of vision	32	12	6	1	11	0	0	2
	27%	34%	33%	7%	31%	0%	0%	40%
Redness in the eye	24	6	7	0	6	1	4	0
	20%	17%	39%	0%	17%	20%	80%	0%
Eye pain	32	10	5	2	11	1	3	0
	27%	29%	28%	13%	31%	20%	60%	0%
None of these	3	1	0	1	1	0	0	0

	3%	3%	0%	7%	3%	0%	0%	%
I don't know/ I am not sure	27	4	1	8	10	2	0	2
	23%	11%	6%	53%	29%	40%	0%	40%
All correct responses (with or without other responses)	*9*	*5*	*0*	*0*	*3*	*0*	*0*	*1*
	8%	*14%*	*0%*	*0%*	*9%*	*0%*	*0%*	*20%*
One or more correct responses	*79*	*29*	*16*	*6*	*20*	*3*	*2*	*3*
	67%	*83%*	*89%*	*40%*	*57%*	*60%*	*40%*	*60%*

Green cells indicate correct responses.

Table 10-47 shows responses for P-13 (symptoms indicating infection). There were four correct answers to this question, including fever (48% selected), flu-like symptoms (23%), headache with or without stiff neck (42%) and nausea and/or confusion (44%). 8% of patients/caregivers selected all the correct answers, although 72% selected at least one correct answer.

Table 10-47 Detailed response to P-Q13 – What are the symptoms that may mean you are experiencing an infection including brain infection?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Fever	57	26	7	2	12	4	4	2
	48%	74%	39%	13%	34%	80%	80%	40%
Flu-like symptoms	27	14	2	2	4	0	3	2
	23%	40%	11%	13%	11%	0%	60%	40%
Headache with or without stiff neck	50	17	12	2	9	3	5	2
	42%	49%	67%	13%	26%	60%	100%	40%
Nausea and/or confusion	52	25	9	4	8	2	2	2
	44%	71%	50%	27%	23%	40%	40%	40%
Swelling of the extremities due to accumulation of water	25	10	4	2	8	1	0	0
	21%	29%	22%	13%	23%	20%	0%	0%
None of these	4	1	0	2	1	0	0	0
	3%	3%	0%	13%	3%	0%	0%	0%
I don't know/ I am not sure	27	3	4	7	11	1	0	1
	23%	9%	22%	47%	31%	20%	0%	20%
All correct responses (with or without other responses)	*10*	*9*	*0*	*0*	*0*	*0*	*0*	*1*
	8%	*26%*	*0%*	*0%*	*0%*	*0%*	*0%*	*20%*
	85	*31*	*14*	*6*	*21*	*4*	*5*	*4*

One or more correct responses	*72%*	*89%*	*78%*	*40%*	*60%*	*80%*	*100%*	*80%*

Green cells indicate correct responses.

Table 10-48 shows responses for P-Q14 (symptoms indicating impaired liver function). There were seven correct answers for this question, and 3% of patients/caregivers correctly selected all seven. 'Yellowing of the eyes or skin' (50%) and dark urine (43%) were the most selected responses. 80% of patients/caregivers selected at least one correct answer.

Table 10-48 Detailed response to P-Q14 – What are the symptoms that may mean you may be experiencing impaired liver function?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Unexplained nausea	28	7	4	2	8	5	0	2
	24%	20%	22%	13%	23%	100%	0%	40%
Vomiting	36	8	10	1	8	4	3	2
	31%	23%	56%	7%	23%	80%	60%	40%
Abdominal/Stomach pain	49	19	11	2	9	2	3	3
	42%	54%	61%	13%	26%	40%	60%	60%
Fatigue/Tiredness (overall feeling of tiredness or lack of energy)	43	15	10	4	7	4	1	2
	36%	43%	56%	27%	20%	80%	20%	40%
Rash (change in the color or in the texture of your skin that can cause itchiness)	27	14	3	3	3	3	0	1
	23%	40%	17%	20%	9%	60%	0%	20%
Yellowing of the eyes or the skin	59	27	7	5	14	4	0	2
	50%	77%	39%	33%	40%	80%	0%	40%
Dark urine	51	9	16	4	12	4	3	3
	43%	26%	89%	27%	34%	80%	60%	60%
Headache	24	13	4	1	2	3	1	0
	20%	37%	22%	7%	6%	60%	20%	0%
Fever	28	16	3	3	2	3	1	0
	24%	46%	17%	20%	6%	60%	20%	0%
Productive cough	3	1	1	0	1	0	0	0
	3%	3%	6%	0%	3%	0%	0%	0%
Blurred vision	10	3	1	2	2	0	1	1
	8%	9%	6%	13%	6%	0%	20%	20%
Joint pain	23	8	6	2	4	0	3	0

	19%	23%	33%	13%	11%	0%	60%	0%
None of these	2	1	0	0	1	0	0	0
	2%	3%	0%	0%	3%	0%	0%	0%
I don't know/ I am not sure	19	2	1	6	8	0	0	2
	16%	6%	6%	40%	23%	0%	0%	40%
All correct responses (with or without other responses)	*3*	*1*	*0*	*0*	*0*	*1*	*0*	*1*
	3%	*3%*	*0%*	*0%*	*0%*	*20%*	*0%*	*20%*
One or more correct responses	*94*	*32*	*17*	*9*	*24*	*5*	*4*	*3*
	80%	*91%*	*94%*	*60%*	*69%*	*100%*	*80%*	*60%*

Green cells indicate correct responses.

Table 10-49 shows responses for P-Q15 (skin conditions to report to the doctor). There were two correct answers to this question, which were selected by 51% and 59% of patients/caregivers, with 34% selecting both correct answers, and 76% selecting at least one. Whilst almost a quarter of patients/caregivers incorrectly selected 'dryness' (23%), there were only 3% who selected 'none of these', indicating the majority would report unusual skin conditions to their doctor.

Table 10-49 Detailed response to P-Q15 – Which skin conditions, if any, should be reported immediately to your doctor?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Skin nodules (e.g. shiny or pearly nodules)	60	18	11	9	14	4	4	0
	51%	51%	61%	60%	40%	80%	80%	0%
Patches or open sores that do not heal within a few weeks	70	27	10	8	16	4	2	3
	59%	77%	56%	53%	46%	80%	40%	60%
Dryness	27	10	4	3	6	0	4	0
	23%	29%	22%	20%	17%	0%	80%	0%
None of these	4	2	0	0	2	0	0	0
	3%	6%	0%	0%	6%	0%	0%	0%
I don't know/ I am not sure	20	2	4	4	8	0	0	2
	17%	6%	22%	27%	23%	0%	0%	40%
At least one correct response	*90*	*31*	*14*	*11*	*21*	*5*	*5*	*3*
	76%	*89%*	*78%*	*73%*	*60%*	*100%*	*100%*	*60%*
Both correct responses (with or without other responses)	*40*	*14*	*7*	*6*	*9*	*3*	*1*	*0*
	34%	*40%*	*39%*	*40%*	*26%*	*60%*	*20%*	*0%*

Green cells indicate correct responses

Table 10-50 Detailed response to P-Q16 – You should avoid exposure to sunlight without protection while on Mayzent (siponimod).

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	87	27	15	6	26	5	5	3
	74%	77%	83%	40%	74%	100%	100%	60%
No	8	3	1	0	3	0	0	1
	7%	9%	6%	0%	9%	0%	0%	20%
I don't know/ I am not sure	23	5	2	9	6	0	0	1
	19%	14%	11%	60%	17%	0%	0%	20%

Green cells indicate correct response.

Table 10-51 shows responses for P-Q19 (number of missed dose days that would require a new starter pack). There was only one correct answer to this question (4 consecutive days), which was selected by 27% of patients/caregivers, with a further 26% selecting 3 consecutive days. The most common response to this question was 'I don't know/I'm not sure', selected by 32% of patients/caregivers.

Table 10-51 Detailed response to P-Q19 – 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 Mayzent (siponimod) treatment be interrupted before you need to contact your doctor and reinitiate treatment with a new starter pack?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**118**	**35**	**18**	**15**	**35**	**5**	**5**	**5**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
3 consecutive days	31	12	2	3	6	1	4	3
	26%	34%	11%	20%	17%	20%	80%	60%
4 consecutive days	32	7	7	5	9	1	1	2
	27%	20%	39%	33%	26%	20%	20%	40%
One full week	17	8	4	1	4	0	0	0
	14%	23%	22%	7%	11%	0%	0%	0%
I don't know/ I am not sure	38	8	5	6	16	3	0	0
	32%	23%	28%	40%	46%	60%	0%	0%

Green cells indicate correct response.

10.4.13 Risk of pregnancy (Patient/Caregiver)

Questions relating to risk of pregnancy were only asked to female patients of childbearing age, or their caregivers.

Figure 14 shows patient/caregiver responses to each question pertaining to knowledge of potential risks of pregnancy. The patient/caregiver survey showed that the question relating to avoiding getting pregnant was answered correctly by more than 70% with the remaining question relating to contraception after stopping treatment achieving less than 70% correct responses.

Figure 14. Risk of pregnancy – patient/caregiver responses

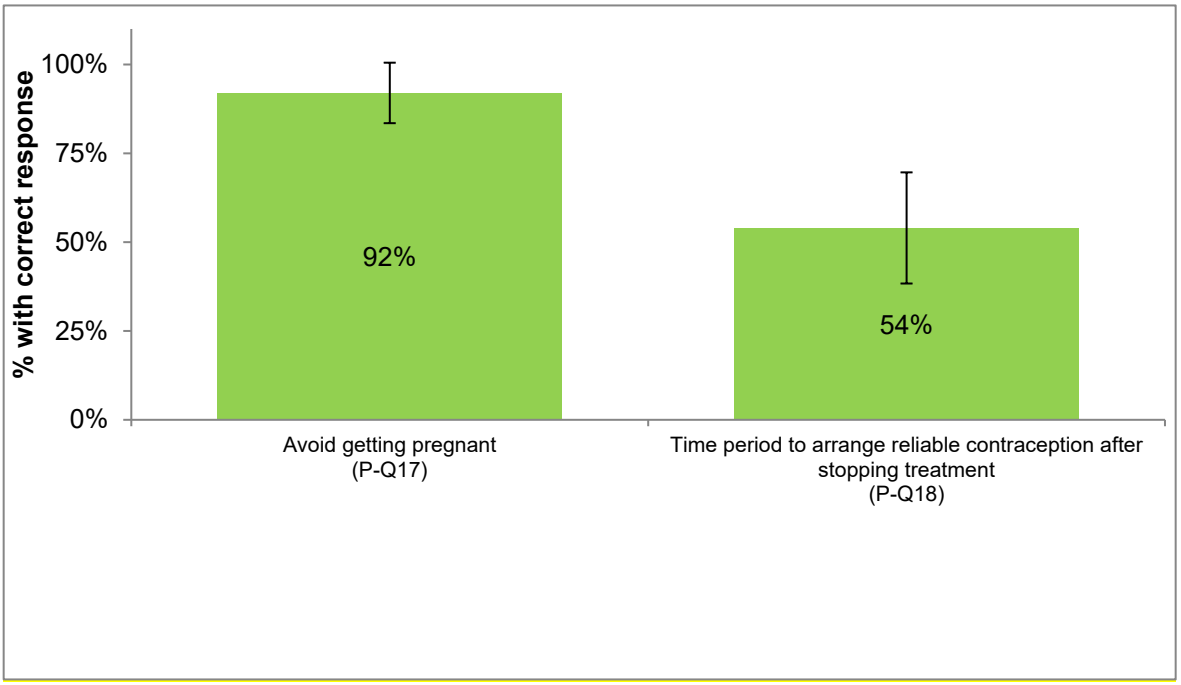


Table 10-52 Detailed response to P-Q17 – You must avoid getting pregnant while on Mayzent (siponimod).

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**39**	**11**	**6**	**6**	**9**	**1**	**5**	**1**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
Yes	36	10	5	6	8	1	5	1
	92%	91%	83%	100%	89%	100%	100%	100%
No	2	1	0	0	1	0	0	0
	5%	9%	0%	0%	11%	0%	0%	0%
I don't know/ I am not sure	1	0	1	0	0	0	0	0
	3%	0%	17%	0%	0%	0%	0%	0%

Green cells indicate correct response.

Table 10-53 shows responses for P-Q18 (length of time effective contraception is required after stopping siponimod). There was only one correct answer aligned with the educational materials (10 days), which was selected by 44% of patients/caregivers, with 54% selecting a response of 10 days or more.

Table 10-53 Detailed response to P-Q18 – For how many days after stopping treatment with Mayzent (siponimod) should you arrange reliable methods of birth control with consultation from your doctor?

	Country							
	Base	**DE**	**NL**	**HR**	**ES**	**SE**	**DK**	**CA**
Base	**39**	**11**	**6**	**6**	**9**	**1**	**5**	**1**
	100%	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***
6 days	3	1	0	1	1	0	0	0
	8%	9%	0%	17%	11%	0%	0%	0%
10 days	17	6	2	0	4	1	4	0
	44%	55%	33%	0%	44%	100%	80%	0%
12 days	4	1	2	0	0	0	1	0
	10%	9%	33%	0%	0%	0%	20%	0%
I don’t know/ I am not sure	15	3	2	5	4	0	0	1
	38%	27%	33%	83%	44%	0%	0%	100%
At least 10 days	*21*	*7*	*4*	*0*	*4*	*1*	*5*	*0*
	54%	*64%*	*67%*	*0%*	*44%*	*100%*	*100%*	*0%*

Green cells indicate correct response.

10.5 Other analyses

Sub-group analysis has been conducted to investigate the impact of receipt of materials, differences by HCP role and regional variation.

10.5.1 Impact of receipt of educational materials

Table 10-54 shows a summary of correct responses at each question, for patients/caregivers who recall receipt of educational materials compared to those who do not recall receipt. Patients/caregivers who recalled receiving educational materials for Mayzent demonstrated consistently higher knowledge across all topics compared to those who did not receive materials or were unsure. In particular, the patient/caregivers who confirmed receipt of materials showed a significantly higher level of correct responses to 9/18 questions, including blood tests prior to initiation (P-Q2), need for ECG in patients at risk (P-Q5), skin examinations (P-Q6), monitoring duration after first dose (P-Q7), reasons for extended monitoring (P-Q8), symptoms of brain infection (P-Q13) or liver impairment (P-Q14), reporting of skin conditions (P-Q15) and exposure to sunlight (P-Q16).

A more detailed breakdown of responses to questions with multiple correct responses is included in Appendix 4. Notably, for some questions, a significantly higher proportion of patients/caregivers who had not received educational materials selected “I don’t know/I am not sure” as their response. This was seen for P-Q2 (38% vs 6%, p=0.00001), P-Q4 (40% vs 15%, p=0.002), P-Q6 (44% vs 11%, p=0.00003), P-Q7 (31% vs 6%, p=0.002), P-Q13 (37% vs 12%, p=0.002), P-Q14 (25% vs 9%, p=0.02), and P-Q15 (31% vs 6%, p=0.0004).

These findings highlight the positive impact of educational materials on patient/caregiver understanding of key information when treated with Mayzent.

Table 10-54 Patient/caregivers knowledge based on receipt of the educational materials

	Clinically meaningful correct response			
	Confirmed Receipt of materials	**Materials not received (or unsure if materials received)**	**Total**	*p value*
Base	**66**	**52**	**118**	
Q2. For what reasons will the doctor do a blood test before you get ready for your treatment with Mayzent (siponimod)?	9 14%	1 2%	10 8%	*p = 0.02*
Q3. 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)?	39 59%	23 44%	62 53%	*p = 0.11*
Q4. For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with Mayzent (siponimod)?	6 9%	3 6%	9 8%	*p = 0.50*
Q5. 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)	55 83%	33 63%	88 75%	*p = 0.01*
	13	1	14	*p = 0.003*

Q6. When, if at all, may your doctor want to conduct a skin examination?	20%	2%	12%	
Q7. At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask you to stay in the clinic after taking the first dose so that your blood pressure and pulse can be monitored?	37 77%	15 43%	52 63%	*p = 0.001*
Q8. 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?	37 56%	15 29%	52 44%	*p = 0.003*
Q9. Are you aware that there is a period of titration/ up-dosing at the start of treatment with Mayzent (siponimod).	58 88%	39 75%	97 82%	*p = 0.07*
Q10. For how many days is the titration / up-dosing schedule (pack)?	35 53%	23 44%	58 49%	*p = 0.34*
Q11. 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	41 62%	26 50%	67 57%	*p = 0.19*
Q12. 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)?	48 73%	31 60%	79 67%	*p = 0.13*
Q13. What are the symptoms that may mean you are experiencing an infection including brain infection?	54 82%	31 60%	85 72%	*p = 0.008*
Q14. What are the symptoms that may mean you may be experiencing impaired liver function?	58 88%	36 69%	94 80%	*p = 0.01*
Q15. Which skin conditions, if any, should be reported immediately to your doctor?	58 88%	32 62%	90 76%	*p =0.0008*
Q16. You should avoid exposure to sunlight without protection while on Mayzent (siponimod).	54 82%	33 63%	87 74%	*p = 0.02*
Q17. *(Female patients of childbearing age only)* You must avoid getting pregnant while on Mayzent (siponimod).	21 95%	15 88%	36 92%	*Base size too small for testing*
Q18. *(Female patients of childbearing 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?	15 68%	6 35%	21 54%	*Base size too small for testing*
	20	12	32	*p = 0.38*

Q19. 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 Mayzent (siponimod) treatment be interrupted before you need to contact your doctor and reinitiate treatment with a new starter pack?	30%	23%	27%

HCPs level of receipt of educational materials was higher than for patients/caregivers, and those recalling receipt of materials were more likely to give correct responses to most but not all questions. HCPs who recalled receiving the materials were significantly more likely to select correct responses for ten questions, indicating greater knowledge relating to patient identification (H-Q3), titration (H-Q11, H-Q12, H-Q14), ECG findings requiring extended monitoring (H-Q18), first dose monitoring (H-Q19), ophthalmic examination (H-Q21), delay of treatment initiation following VZV vaccination (H-Q25), length of time Mayzent remains in the blood after treatment discontinuation (H-Q27), and how long female patients should use effective contraception following Mayzent discontinuation (H-Q28).

For some questions, a significantly greater proportion of HCPs who had not received educational materials selected “I don’t know/I am not sure.” This was observed for Q16 (15% vs 4%, p=0.02), Q18 (21% vs 9%, p=0.049), Q20 (29% vs 10%, p=0.002), and Q29 (26% vs 7%, p=0.0005). This pattern indicates that educational materials not only improve correct knowledge but also reduce uncertainty among HCPs, echoing the trend observed among patients and caregivers.

A more detailed breakdown of responses to questions with multiple correct responses is included in Appendix 5.

Table 10-55 HCPs knowledge based on receipt of the educational materials

	Clinically meaningful correct response			
	Confirmed receipt of materials	**Materials not received/unsure**	**Total**	*p value*
Base	**186**	**34**	**220**	
Q3. Prior to commencing treatment with Mayzent (siponimod), the CYP2C9 genotype of every patient should be determined	168 90%	22 65%	190 86%	*p= 0.006*
Q4. Which of the following maintenance doses is correct for the initiation of Mayzent ((siponimod) for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?	92 49%	11 32%	103 47%	*p = 0.07*
Q5. Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?	121 65%	17 50%	138 63%	*p = 0.10*
Q6. When initiating treatment with Mayzent (siponimod) you have to conduct baseline electrocardiogram (ECG) in patients with sinus bradycardia (heart rate <55 bpm), first or second degree AV block	177 95%	32 94%	209 95%	*p = 0.80*

or a history of myocardial infarction or heart failure				
Q7. When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?	73 39%	16 47%	89 40%	*p = 0.39*
Q8. For which of the following medications/therapies is co-administration not recommended for Mayzent (siponimod)?	115 62%	17 50%	132 60%	*p = 0.20*
Q9. Caution should be taken when switching to Mayzent (siponimod) from other disease modifying therapies due to the risk of additive immune system effects	161 87%	25 74%	186 85%	*p = 0.053*
Q10. Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?	178 96%	30 88%	208 95%	*p = 0.08*
Q11. An up-titration scheme is required for Mayzent (siponimod). Please indicate the number of days this scheme takes to complete.	126 68%	17 50%	143 65%	*p = 0.046*
Q12. When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?	97 52%	9 26%	106 48%	*p = 0.006*
Q13. The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are:	33 18%	2 6%	35 16%	*p = 0.08*
Q14. What steps need to be taken if a dose is missed for more than one day during the first 6 days treatment initiation?	108 58%	12 35%	120 55%	*p = 0.01*
Q15. Have you counselled your patients on the importance of taking their daily dose of Mayzent (siponimod), during both titration and maintenance phases of treatment?	183 98%	32 94%	215 98%	*p = 0.12*
Q16. For which type/s of patients is Mayzent (siponimod) not recommended?	17 9%	4 12%	21 10%	*p = 0.63*
Q17. How many hours should a patient with sinus bradycardia, 1st /2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?	124 67%	19 56%	143 65%	*p = 0.23*
Q18. 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?	108 58%	13 38%	121 55%	*p = 0.03*
	181	30	211	*p = 0.01*

Q19. Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other specialized MS center for FDM?	97%	88%	96%	
Q20. For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?	67 36%	11 32%	78 35%	*p = 0.68*
Q21. At what time after starting treatment should a full ophthalmologic evaluation be performed?	105 56%	13 38%	118 54%	*p = 0.05*
Q22. Patients receiving Mayzent (siponimod) should be counselled to report signs and symptoms of infection immediately to their prescriber	178 96%	32 94%	210 95%	*p = 0.68*
Q23. Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection	171 92%	29 85%	200 91%	*p = 0.22*
Q24. You should check varicella zoster virus antibody status in patients receiving Mayzent (siponimod) without a healthcare professionally confirmed history of chicken pox	170 91%	31 91%	201 91%	*p = 0.97*
Q25. Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?	149 80%	22 65%	171 78%	*p = 0.047*
Q26. What action should be taken if a patient reports serious infection during treatment on Mayzent (siponimod)?	137 74%	20 59%	157 71%	*p = 0.08*
Q27. After stopping treatment, for how long does Mayzent (siponimod) remain in the blood?	70 38%	6 18%	76 35%	*p = 0.02*
Q28. For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod)? For at least…	111 60%	14 41%	125 57%	*p = 0.045*
Q29. For patients who become pregnant during treatment, what is the correct approach from the options below?	135 73%	19 56%	154 70%	*p = 0.051*
Q30. What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?	105 56%	20 59%	125 57%	*p = 0.80*

10.5.2 Impact of HCP role

There were some differences in responses between neurologists and MS specialist nurses, with neurologists demonstrating a higher level of knowledge regarding the key messages in the educational

materials. In particular, knowledge of patient identification (H-Q3), dosing (H-Q4, H-Q12), medications not recommended for co-administration (H-Q8), timing of pre-treatment liver function testing (H-Q10), first dose monitoring (H-Q18, H-Q19), delay after VZV vaccination (H-Q25), and the correct approach when a patient becomes pregnant during treatment (H-Q29) is significantly higher among neurologists.

However, for most questions there is no significant difference in the level of correct responses by role, indicating that overall the materials are equally effective for nurses and neurologists.

Table 10-56 HCPs knowledge comparing responses for Neurologists and MS Nurses

	Neurologists	**MS Nurses**	*p value*
Base	**161**	**59**	
Q3. Prior to commencing treatment with Mayzent (siponimod), the CYP2C9 genotype of every patient should be determined	144 89%	46 78%	*p = 0.03*
Q4. Which of the following maintenance doses is correct for the initiation of Mayzent (siponimod) for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?	84 52%	19 32%	*p = 0.009*
Q5. Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?	105 65%	33 56%	*p = 0.21*
Q6. When initiating treatment with Mayzent (siponimod) 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	152 94%	57 97%	*p = 0.51*
Q7. When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?	67 42%	22 37%	*p = 0.56*
Q8. For which of the following medications/therapies is co-administration not recommended for Mayzent (siponimod)?	104 65%	28 28%	*p = 0.02*
Q9. Caution should be taken when switching to Mayzent (siponimod) from other disease modifying therapies due to the risk of additive immune system effects	139 86%	47 80%	*p = 0.23*
Q10. Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?	157 98%	51 86%	*p = 0.001*
Q11. An up-titration scheme is required for Mayzent (siponimod). Please indicate the number of days this scheme takes to complete.	107 66%	36 61%	*p = 0.45*
Q12. When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?	84 52%	22 37%	*p = 0.05*
	26	9	*p = 0.87*

Q13. The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are:	16%	15%	
Q14. What steps need to be taken if a dose is missed for more than one day during the first 6 days treatment initiation?	85 53%	35 59%	*p = 0.39*
Q15. Have you counselled your patients on the importance of taking their daily dose of Mayzent (siponimod), during both titration and maintenance phases of treatment?	159 99%	56 95%	*p = 0.09*
Q16. For which type/s of patients is Mayzent (siponimod) not recommended?	14 9%	7 12%	*p = 0.48*
Q17. How many hours should a patient with sinus bradycardia, 1st /2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?	107 66%	36 61%	*p = 0.45*
Q18. 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?	104 65%	17 29%	*p = 0.000002*
Q19. Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other specialized MS center for FDM?	158 98%	53 90%	*p = 0.006*
Q20. For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?	19 32%	59 37%	*p = 0.54*
Q21. At what time after starting treatment should a full ophthalmologic evaluation be performed?	27 46%	91 57%	*p = 0.16*
Q22. Patients receiving Mayzent (siponimod) should be counselled to report signs and symptoms of infection immediately to their prescriber	152 94%	58 98%	*p = 0.22*
Q23. Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection	149 93%	51 86%	*p = 0.16*
Q24. You should check varicella zoster virus antibody status in patients receiving Mayzent (siponimod) without a healthcare professionally confirmed history of chicken pox	149 93%	52 88%	*p = 0.30*
Q25. Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?	133 83%	38 64%	*p = 0.004*
Q26. What action should be taken if a patient reports serious infection during treatment on Mayzent (siponimod)?	116 72%	41 69%	*p = 0.71*
	60	16	*p = 0.16*

Q27. After stopping treatment, for how long does Mayzent (siponimod) remain in the blood?	37%	27%	
Q28. For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod)? For at least…	97 60%	28 47%	*p = 0.09*
Q29. For patients who become pregnant during treatment, what is the correct approach from the options below?	121 75%	33 56%	*p = 0.006*
Q30. What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?	95 59%	30 51%	*p = 0.28*

Table 10-57 Sample demographics (HCPs Split by Specialty)

		Specialty	
	Total	**Neurologists**	**MS Nurses**
N =	220	161	59
S3. Practice hospital type			
Hospital Only	116 (53%)	83 (52%)	33 (56%)
Hospital and Office	84 (38%)	69 (43%)	15 (25%)
Private office only	20 (9%)	9 (6%)	11 (19%)
S3a. Primary hospital type (hospital-based HCPs only)			
Teaching/University hospital	138 (69%)	107 (70%)	31 (65%)
Public non-teaching (general) hospital	59 (30%)	43 (28%)	16 (33%)
Private hospital	3 (2%)	2 (1%)	1 (2%)
S5. Number of patients treated with relapsing remitting multiple sclerosis in last three months (excl. outliers)			
1-49	84 (39%)	47 (30%)	37 (64%)
50-149	80 (37%)	70 (45%)	10 (17%)
150+	50 (23%)	39 (25%)	11 (19%)
Min. (no. patients)	2	4	2
Max (no. patients)	600	600	500
Mean (no. patients)	100	109	75
Standard deviation	112	111	115
Median	60	80	30
S6. Number of patients treated with Secondary progressive multiple sclerosis in last three months (excl. outliers)			
1-49	154 (72%)	108 (69%)	46 (79%)
50-149	46 (21%)	37 (24%)	9 (16%)
150-250	15 (7%)	12 (8%)	3 (5%)
Min. (no. patients)	1	1	1

Max (no. patients)	350	350	300
Mean (no. patients)	44	48	33
Standard deviation	61	64	51
Median	20	25	14
S7. SPMS patients on Mayzent to date (excl. outliers)			
1-20	161 (75%)	111 (71%)	50 (86%)
21-49	30 (14%)	26 (17%)	4 (7%)
50+	24 (11%)	20 (13%)	4 (7%)
Min. (no. patients)	1	1	1
Max (no. patients)	300	300	150
Mean (no. patients)	23	26	15
Standard deviation	45	49	29
Median	7	10	5

10.5.3 Impact of EU region

Responses from patients/caregivers and HCPs in Northern and Southern Europe have been compared (see Table 10-58 and Table 10-59). There are no consistent regional patterns in responses. For patients/ caregivers there are nine questions where there is a significant difference between regions, with Northern Europe scoring higher (P-Q3, P-Q5, P-Q7, P-Q8, P-Q12, P-Q13, P-Q14, P-Q15, P-Q16). For HCPs there are three questions where there are significant differences between regions, H-Q8 and H-Q20 with Southern Europe scoring higher and H-Q29 with Northern Europe scoring higher.

Results indicate that the materials are equally effective across European regions.

Table 10-58 Patient/caregivers knowledge based on their regional location (EU only)

	N. Europe (DE, NL, DK, SE)	**S. Europe (HR, ES)**	*p value*
Base	**63**	**50**	
Q2. For what reasons will the doctor do a blood test before you get ready for your treatment with Mayzent (siponimod)?	12 19%	2 4%	*p = 0.02*
Q3. 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)?	42 67%	20 40%	*p = 0.005*
Q4. For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with Mayzent (siponimod)?	6 10%	3 6%	*p = 0.49*

Q5. 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)	54 86%	32 64%	*p = 0.007*
Q6. When, if at all, may your doctor want to conduct a skin examination?	9 14%	5 10%	*p = 0.49*
Q7. At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask you to stay in the clinic after taking the first dose so that your blood pressure and pulse can be monitored?	38 76%	13 42%	*p = 0.002*
Q8. 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?	35 56%	16 32%	*p = 0.01*
Q9. Are you aware that there is a period of titration/ up-dosing at the start of treatment with Mayzent (siponimod).	53 84%	39 78%	*p = 0.41*
Q10. For how many days is the titration / up-dosing schedule (pack)?	33 52%	23 46%	*p = 0.50*
Q11. 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	37 59%	25 50%	*p = 0.35*
Q12. 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)?	50 79%	26 52%	*p =0.002*
Q13. What are the symptoms that may mean you are experiencing an infection including brain infection?	54 86%	27 54%	*p =0.0002*
Q14. What are the symptoms that may mean you may be experiencing impaired liver function?	58 92%	33 66%	*p =0.0005*
Q15. Which skin conditions, if any, should be reported immediately to your doctor?	55 87%	32 64%	*p =0.0035*
Q16. You should avoid exposure to sunlight without protection while on Mayzent (siponimod).	52 83%	32 64%	*p = 0.03*
Q17. *(Female patients of childbearing age only)* You must avoid getting pregnant while on Mayzent (siponimod).	21 91%	14 93%	*Base size too small for testing*

Q18. *(Female patients of childbearing 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?	17 74%	4 27%	*Base size too small for testing*
Q19. 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 Mayzent (siponimod) treatment be interrupted before you need to contact your doctor and reinitiate treatment with a new starter pack?	16 25%	14 28%	*p = 0.76*

Table 10-59 HCPs knowledge based on their regional location (EU only)

	N. Europe (DE, NL, SE, DK)	**S. Europe (ES, HR)**	*p value*
Base	**105**	**95**	
Q3. Prior to commencing treatment with Mayzent (siponimod), the CYP2C9 genotype of every patient should be determined	86 82%	84 88%	*p = 0.20*
Q4. Which of the following maintenance doses is correct for the initiation of Mayzent (siponimod) for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3?	49 47%	45 47%	*p = 0.92*
Q5. Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?	63 60%	59 62%	*p = 0.14*
Q6. When initiating treatment with Mayzent (siponimod) 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	99 94%	90 95%	*p = 0.89*
Q7. When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?	40 38%	44 46%	*p = 0.24*
Q8. For which of the following medications/therapies is co-administration not recommended for Mayzent (siponimod)?	52 50%	61 64%	*p = 0.04*
Q9. Caution should be taken when switching to Mayzent (siponimod) from other disease modifying therapies due to the risk of additive immune system effects	85 81%	86 91%	*p = 0 .055*
Q10. Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?	98 93%	91 96%	*p = 0.45*

Q11. An up-titration scheme is required for Mayzent (siponimod). Please indicate the number of days this scheme takes to complete.	65 62%	68 72%	*p = 0.15*
Q12. When will a patient increase to 3x0.25 mg once daily dosing in the up-titration schedule?	51 49%	46 48%	*p = 0.98*
Q13. The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are:	12 11%	18 19%	*p = 0.14*
Q14. What steps need to be taken if a dose is missed for more than one day during the first 6 days treatment initiation?	52 50%	58 61%	*p = 0.10*
Q15. Have you counselled your patients on the importance of taking their daily dose of Mayzent (siponimod), during both titration and maintenance phases of treatment?	101 96%	95 100%	*p = 0.055*
Q16. For which type/s of patients is Mayzent (siponimod) not recommended?	6 6%	12 13%	*p = 0.09*
Q17. How many hours should a patient with sinus bradycardia, 1st /2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?	107 66%	36 61%	*p = 0.45*
Q18. 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?	55 52%	56 59%	*p = 0.35*
Q19. Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other specialized MS center for FDM?	100 95%	92 97%	*p = 0.56*
Q20. For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?	31 30%	42 44%	*p = 0.03*
Q21. At what time after starting treatment should a full ophthalmologic evaluation be performed?	55 52%	48 51%	*p = 0.79*
Q22. Patients receiving Mayzent (siponimod) should be counselled to report signs and symptoms of infection immediately to their prescriber	98 93%	93 98%	*p = 0.12*
Q23. Patients receiving Mayzent (siponimod) should be cautioned against exposure to sunlight without protection	91 87%	90 95%	*p = 0.052*
Q24. You should check varicella zoster virus antibody status in patients receiving Mayzent (siponimod) without a healthcare professionally confirmed history of chicken pox	93 89%	88 93%	*p = 0.33*

Q25. Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiation?	77 73%	76 80%	*p = 0.86*
Q26. What action should be taken if a patient reports serious infection during treatment on Mayzent (siponimod)?	75 71%	67 71%	*p = 0.89*
Q27. After stopping treatment, for how long does Mayzent (siponimod) remain in the blood?	33 31%	32 34%	*p = 0.73*
Q28. For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod)? For at least…	55 52%	56 59%	*p = 0.35*
Q29. For patients who become pregnant during treatment, what is the correct approach from the options below?	79 75%	57 60%	*p = 0.02*
Q30. What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?	60 57%	49 52%	*p = 0.43*

10.6 Adverse events/adverse reactions

No adverse events were reported from this study.

11 Discussion

The MAH believes that the survey results indicate that, overall, the educational materials are effective at communicating the specific Mayzent (siponimod) safety measures, although some gaps in knowledge have been identified for HCPs and patients/caregivers.

It should be noted that overall success has been measured based on clinically meaningful results, and not always by the strictest criteria, i.e. taking the proportion of respondents who selected all correct responses and no incorrect responses, or selecting an exact response which is aligned with the educational materials. The proportion of HCPs and patients/caregivers selecting some but not all the correct responses, or selecting a clinically more conservative response, is often higher, indicating good knowledge based on clinical experience and judgement. There were 8 questions for HCPs and 7 questions for patients/caregivers that had multiple correct responses and represent a more robust test of knowledge than a single response question and are more difficult for HCPs or patients/caregivers to be classified as fully correct due to the need to select all correct responses.

Patients/caregivers have awareness of some symptoms to report and, based on the criteria of selecting at least one correct response, these questions achieve the 70% threshold for success. However, the proportion of patients/caregivers with awareness of all symptoms is low.

Although knowledge in some areas did not meet the designated threshold, it was unclear if the respondents were completing the survey from recall/memory or were using the EMs while responding. The necessary information is available to HCPs and patients/caregivers in the label and patient information pack insert, in addition to being clearly explained in the educational materials. This is supported by the evidence that knowledge is higher among HCPs and patients/caregivers who recall

receiving the educational materials, which demonstrates that the materials are effective at communicating the important safety information for Mayzent.

All questions that scored below the 70% threshold of correct responses across either the HCP or patient/caregiver surveys have been categorized into high, medium or low risk based on their potential impact on patient management and safety, and the observed pattern of responses, taking into account whether there was a single correct response, or multiple correct responses.

The observed pattern of responses provides additional insight into the level of knowledge. For questions where incorrect responses are dispersed across incorrect options, this indicates a general lack of knowledge, whereas if incorrect responses are focused on one specific incorrect response, this may indicate misunderstanding of the key message.

The remainder of this discussion will review each of these questions and validate their risk categorization.

11.1 Key results

With respect to the objective of assessing the dissemination of the educational materials, results indicate this objective was met for HCPs, with 85% having received the prescribers checklist, and 75% receiving the patient reminder cards. However, patients/caregivers had lower recall of receiving the educational materials, with 56% recalling receiving these.

The proportion of correct responses from HCPs and patient/caregivers across the remaining questions included in the surveys shows the level of knowledge required for the use of Mayzent. Among HCPs, 75% (21/28) of the survey questions had 50% or more correct responses. This included 12/28 questions that had 70% or more correct responses and these were all questions that required a single correct response. Furthermore, 7/28 questions demonstrated a strong level of knowledge, with 90% or more of HCPs responding correctly. Topics HCPs demonstrated good knowledge of include the need to determine CYP2C9 genotype, requirement for an ECG prior to initiation, risk of additive immune effects, timeframe to check liver transaminases, need to counsel patients on taking daily dose, first dose monitoring, counsel patients to report signs of infection, caution against sunlight, need to check VZV antibody status and the timeframe to delay treatment following VZV vaccination, actions needed if a patient has a serious infection, and the correct approach if a patient becomes pregnant.

Among HCPs who recall receiving the educational materials there are still 12/28 questions with 70% or more correct responses, including 8/28 achieving 90% or more.

There were 9/28 questions with 50–69% correct responses (4 with multiple correct responses, and 5 with a single correct response). There were also 7/28 questions with less than 50% correct responses (4 with multiple correct responses and 3 with a single correct response). Topics where knowledge was below 50% include the correct maintenance dose for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3, appropriate timing for skin examinations, specific details of the titration schedule, knowledge of all patient types where Mayzent is not recommended, patients requiring an ophthalmologic examination, and the length of time Mayzent remains in the blood following treatment discontinuation.

Among HCPs who recall receiving the educational materials, one additional question scores over 50%, resulting in 10/28 questions with 50-69% correct responses and 6/28 with less than 50%.

Of the 8 questions for HCPs with multiple correct responses that failed to reach the 70% threshold for success, 6 of these had one or more separate correct responses that were selected by 70% or more, indicating HCPs have good knowledge of these topics but failed to meet the criteria for success defined as selecting all correct responses.

In the patient/caregiver survey, 7/18 questions had 70% or more correct responses (3 with multiple correct responses (where selecting one of these was considered correct), and 4 with a single correct response), with only one question achieving 90% or higher. Topics patients/caregivers showed good knowledge of include the need to avoid pregnancy (>90%), need for an ECG prior to initiation, need for

dose titration, symptoms of infection or liver impairment, skin conditions to report to their doctor, and the need to avoid exposure to sunlight.

Among patients/caregivers who recall receiving the educational materials, there are 9/18 questions with 70% or more correct responses, including one question over 90%.

5/18 questions had 50–69% correct responses (1 with multiple correct responses, and 4 with a single correct response). There were 6/18 questions with less than 50% correct responses (3 with multiple correct responses, and 3 with a single correct response). Topics where knowledge was below 50% include blood tests required prior to initiation, need for eye examinations, reasons for extended monitoring at first dose, timing of skin examination, duration of titration, and number of days can skip maintenance dose.

Among patients/caregivers who recall receiving the educational materials, there are 5/18 questions with 50-69% correct responses and 6/18 questions with less than 50% correct.

Of the 5 questions for patients/caregivers with multiple correct responses that failed to reach the 70% threshold for success, none of these had any separate correct responses that were selected by 70% of more. All questions that scored below 70% have been further categorized by their potential risk impact and are discussed in Section 11.3 (Interpretation).

11.2 Limitations

A limitation of the research method is recognized within this study as the number of HCPs or patients/caregivers evaluated are considered representative of the whole - i.e., it is not feasible to survey every single HCP involved in Mayzent management or every patient treated with Mayzent within any country.

There was a low level of response to the initial survey invitation among both HCPs and patients/caregivers. The lack of data available for non-responders is a limitation in the ability to demonstrate the representativeness of the sample.

The design of some survey questions may limit the likelihood of respondents achieving the required level of success. In order to be a robust test of knowledge, some additional incorrect response options (that were close or closely related to the correct responses) were included in questions where there were multiple correct responses. For some questions, selection of one or more of those distractors, in addition to the correct responses, classifies the individual as having responded incorrectly, even if they demonstrated good knowledge of the topic. For other questions, individuals had to select all of the correct responses to be considered fully correct. In the interpretation, selection of each individual correct response has also been considered.

When asking HCPs to confirm receipt of educational materials, the absence of an explicit 'I don't know' response option may have constrained participants' ability to accurately reflect their uncertainty.

HCPs and patients/caregivers completing the survey were not instructed to refer to the educational materials, and it is therefore unknown whether responses are based on reference to the materials or participant recall. HCPs may have responded based on their own clinical experience, which may not fully align with the educational materials. However, some real-world clinical practices may be more cautious than are required, which does not present a risk to patient safety.

For patients/caregivers, only a proportion of the sample recall receiving the materials and it is unknown how much time has elapsed since receipt. Patients/caregivers can only respond based on their own personal experience, whereas HCPs will be able to draw on experience from multiple patients receiving Mayzent (and other S1P receptor modulators with similar known safety profiles).

11.3 Interpretation

11.3.1 Patient identification and eligibility

11.3.1.1 High risk

HCPs had good awareness of the need to determine CYP2C9 genotype prior to treatment initiation (H-Q3), but they were insufficiently aware of the correct maintenance dose of Mayzent for patients with a genotype of CYP2C9*1*3 or CYP2C9*2*3 (H-Q4), as only 47% of HCPs responded with the correct answer (1mg) which is below the 70% threshold necessary to demonstrate an optimal level of awareness.

11.3.1.2 Medium/low risk

Patients/caregivers demonstrated low knowledge of requirements prior to starting on Mayzent: Awareness of required blood tests (P-Q2), how long after the full course of chicken pox (VZV) vaccination they must wait to start their treatment (P-Q3), which patients would require eye examinations (P-Q4), and the timeframe for skin examinations (P-Q6) are all below the required threshold for success. However, these are classified as medium-low risk as it would be the responsibility of the prescribing HCP to conduct the required tests and checks to confirm eligibility for treatment. HCP results indicate that in general, HCPs are clinically more cautious when conducting pre-initiation tests than is strictly required by the RMP.

11.3.2 Initiation and first dose

11.3.2.1 High risk

HCPs awareness of the types of patients Mayzent is not recommended for is below the threshold of success (H-Q16). This question had eight correct responses, and only 10% of HCPs selected all of these. There were 4 patient types that were selected by >65% of HCPs (Patients with concomitant treatment with class Ia or class III anti-arrhythmic medications, Patients with QTC prolongation >500 msec, Patients with history of symptomatic bradycardia, Patients with active malignancies), but awareness of the other patients where Mayzent is not recommended was low: Patients with uncontrolled hypertension (selected by 50%), Patients with history of recurrent syncope (36%), Patients treated with beta-blockers (32%), Patients with severe untreated sleep apnoea (27%). It is possible that the patient types with the lowest level of correct response are those that HCPs perceive to be lower risk, based on their clinical practice, although this cannot be confirmed from this survey. Raising awareness of these patient types is important to avoid inappropriate prescribing of Mayzent.

However, in other questions HCPs showed good awareness (95%) of the need for an ECG prior to treatment initiation for patients with some pre-existing CV conditions (H-Q6), and that co-administration with Class Ia and III anti-arrhythmics is not recommended (H-Q8), demonstrating a high level of awareness of the actions required to mitigate the potential risks.

HCPs had some awareness of in which patient types an ophthalmologic examination should be conducted prior to Mayzent initiation (H-Q20), with 60%, 55% and 59% correctly identifying patients with Diabetes Mellitus, Uveitis, and History of retinal disorders respectively, all below the threshold for success. 35% of HCPs correctly identified all three patient types, and so awareness of the need for ophthalmologic examination in some patients could be improved to reduce the risk of macular oedema.

11.3.2.2 Medium risk

HCPs showed some knowledge of the medications/therapies that are not recommended for co-administration with Mayzent (H-Q8). There were two correct answers, “Class Ia and III anti-arrhythmics”

and “Phototherapy with UV-B radiation or PUVA photochemotherapy”, which were selected by 29% and 15% of HCP respectively. However, this question may have been misleading to HCPs as the educational materials advise HCPs to take caution if patients are concomitantly treated with anti-neoplastics, immunomodulatory or immunosuppressive therapies, and so the response for “all of the above” has been considered a correct response. Including those who selected “all of the above” along with those selecting each individual response would take the % selecting “Class Ia and III anti-arrhythmics” to 78% and “Phototherapy with UV-B radiation or PUVA photochemotherapy” to 64%.

HCP knowledge of the need to perform skin examinations every 6-12 months (H-Q7) following initiation is good (75%), but awareness of the need prior to initiation is lower (59%) and below the level required for satisfactory awareness. This has been classified as a medium risk as only 40% of HCPs correctly selected both responses, suggesting some patients’ skin examinations may be delayed.

HCPs demonstrated some knowledge of how long a patient with heart conditions such as sinus bradycardia, 1st/2nd degree AV block or history of myocardial infarction should be monitored at treatment initiation with Mayzent (H-Q17). A total of 55% of HCPs selected the correct answer (six hours) with a further 10% selecting a longer duration, reflecting a more cautious approach to patient monitoring in clinical practice.

HCPs had some knowledge about what finding on the ECG at the end of the 6-hour monitoring period would warrant initiation of additional appropriate management and observation (H-Q18). There were two correct answers to this question, New onset second degree or higher AV block and QTc>500 msec, selected by 71% and 60% of HCPs respectively, with 55% selecting both correct answers. Importantly, one of the incorrect answer options was selected by almost half of respondents (Transient sinus bradycardia of 50 bmp, 48%), and another was selected by more than a quarter (Hypotension, 26%). This would result in a more conservative approach to patient monitoring.

11.3.2.3 Low risk

HCP awareness of the recent test results that should be made available prior to initiating Mayzent treatment was good (H-Q5), with 84% correctly selecting “full blood count” and 74% correctly selecting “Transaminase and bilirubin levels”. 63% of HCPs selected both correct responses, with some HCPs also expecting to conduct additional tests. Whilst not aligned with the educational materials, conducting additional tests does not lead to risk of inappropriate prescribing, and may be part of HCPs’ real world clinical practice.

HCPs demonstrated good knowledge about the time period for checking liver transaminases before commencing patients on Mayzent (H-Q10), with 95% selecting a response “within 6 months”. Although the materials refer to a six-month timeframe, selecting a time period of two or three months reflects a more conservative approach in clinical practice that does not impact on patient safety.

Patients/caregivers with heart problems had an awareness below the 70% threshold level with regard to the appropriate length of time that their HCP would monitor their pulse and blood pressure after they have taken the first dose of Mayzent (P-Q7), with 63% of patients/caregivers selecting the correct answer (at least six hours).

Patients/caregivers also demonstrated low knowledge of the reasons they may need to spend an extended period of time in the clinic being monitored by their HCP after taking the first dose of Mayzent (P-Q8), as less than half of patients/caregivers (44%) selected the correct answer (Your/Their ECG) shows abnormalities.

However, ultimately it is the responsibility of the HCP to be aware of this information and to determine the duration of monitoring and to evaluate the findings, rather than the patient/caregiver, so a low level of awareness among patients/caregivers is a low risk.

11.3.3 Titration

11.3.3.1 Medium risk

Both HCPs and patients/caregivers lacked awareness of the duration of the up-titration schedule (H-Q11, P-Q10), with only 27% of HCPs and 26% of patients/caregivers correctly selecting “five days”, which is well below the 70% threshold necessary to demonstrate an optimal level of awareness. However, as the maintenance dose of 2mg is first given on day six, it could be considered that the titration schedule lasts for 6 days. Including responses of 5 days or 6 days increases the level of correct responses to 65% for HCPs and 49% of patients/caregivers.

HCPs demonstrated insufficient knowledge with regard to when a patient on Mayzent will be increased to a dosage of 3x0.25mg during the up-titration schedule (H-Q12), as only 48% of HCPs responded with the correct answer (day four) and a quarter of HCPs indicated that they did not know the specific day to increase the dose during the up-titration schedule.

HCPs and patients/caregivers were insufficiently aware of the appropriate steps that need to be taken if a patient misses a Mayzent dose for longer than one day during the first six days of their treatment (H-Q14, P-Q11). Only 55% of HCPs and 57% of patients/caregivers responded with the correct answer (The titration schedule needs to be restarted with a new titration pack), which is below the 70% threshold, but still represents a majority (>50%).

However, the format of the titration pack is such that clear daily dosing information is provided on the pack, along with an additional titration guide. These additional materials explain to HCPs and patients/caregivers the daily dosing schedule and the required actions if a dose is missed during the first six days of treatment with Mayzent.

HCPs showed mixed knowledge with regard to the recommended maintenance dose/s for Mayzent after the up-titration schedule (H-Q13), as only 16% of respondents correctly identified both the 1mg and 2mg doses. The majority of HCPs (71%) selected the 2mg dose, which is the correct maintenance dose for most patients. Awareness of the 1mg maintenance dose was lower (27%), although this is only used in specific patient types, and the question did not specify any particular genotype

11.3.4 During treatment

11.3.4.1 High risk

Patients/caregivers demonstrated mixed knowledge with regard to the appropriate symptoms that would indicate they/the patient was experiencing macular oedema (P-Q12), a brain infection (P-Q13), or impaired liver function (P-Q14), which presents potential high risk if patients/ caregivers are unaware of symptoms to be vigilant for and report to their doctor while on treatment.

All of the questions on these topics had multiple correct responses, along with some incorrect responses included as distractor answers. In regard to symptoms of macular oedema, 67% selected at least one correct response. “Blurred or wavy vision” was the most selected correct response (63% of patient/caregivers) but other correct responses had low awareness: Loss of vision (27%), Changes in colour / colour looking faded (21%), and only 8% of patients/caregivers selected all the correct responses.

For symptoms of infection, including brain infection, “fever” was the most selected correct response (48% of patients/caregivers), and 72% selected at least one correct response. Only 8% of patients/caregivers were fully correct in selecting all 4 correct responses.

Patients/caregivers had low awareness of the symptoms of impaired liver function. There were seven correct responses to this question, with all selected by 50% or fewer patients, although 80% selected at least 1 correct response. “Yellowing of the eyes or the skin” was the most selected response (50%), and only 3% of patients/caregivers correctly selected all seven correct responses.

Patients/caregivers demonstrated low knowledge overall with regard to how many days they can interrupt their Mayzent treatment before they need to contact their doctor and reinitiate treatment, after finishing the up-dosing period (P-Q19), as only 27% of patients/caregivers selected the correct answer (4 consecutive days).

11.3.4.2 Medium risk

HCPs demonstrated a low knowledge overall with regard to how long Mayzent remains in the blood after a patient has finished their treatment (H-Q7), as only 35% of respondents answered correctly (10 days).

Patients/caregivers demonstrated some knowledge with regard to which skin conditions they should report immediately to their doctor during Mayzent treatment (P-Q15). There were two correct responses to this question, Patches or open sores that do not heal within a few weeks (selected by 59% of patients/caregivers) and Skin nodules (e.g. shiny or pearly nodules) (51%), with 76% selecting at least one of these options. 34% of patient/caregivers correctly selected both correct responses, but only 3% said they would not report any skin conditions, indicating an expectation that changes in skin condition would be reported to their doctor.

11.3.4.3 Low risk

Both HCPs and patients/ caregivers show high awareness of the need to avoid sunlight without protection while receiving treatment with Mayzent (H-Q23, P-Q16). A total of 91% of HCPs are aware of the need to caution patients against exposure to sunlight, and 74% of patients/caregivers were aware of this risk.

HCPs knowledge of the timeframe for ophthalmologic evaluation after starting treatment was good (H-Q21). 54% selected the correct answer (three to four months), with 15% selecting a shorter timeframe, indicating that most HCPs would perform the examination within the required timeframe.

HCPs had good awareness regarding when patients can be initiated on Mayzent after a full course of vaccination against VZV (H-Q25). A total of 52% of HCPs gave the correct answer of one month, with a further 26% selecting a longer wait period, which is not aligned with the messages in the educational materials but reduces the risk of virus reactivation.

HCPs have good awareness of the need to check varicella zoster virus antibody status in patients receiving Mayzent (H-Q24) without a healthcare professionally confirmed history of chicken pox (91% selected the correct response)

HCP awareness of actions that should be taken if a patient reports serious infection during treatment with Mayzent (H-Q26). 71% correctly selected that both responses were correct: “Perform prompt diagnostic evaluation and initiate appropriate treatment if diagnosed” and “Consider treatment suspension if there are signs and symptoms that may be suggestive of progressive leukoencephalopathy (PML) or cryptococcal meningitis (CM)”.

HCPs have good awareness of the actions required if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (H-Q30). There were two correct responses, “Check liver enzymes” and “Discontinue treatment if significant liver injury is confirmed”, which were selected by 79% and 74% of HCPs respectively. 57% of HCPs selected both options, which represents a majority.

11.3.5 Risk of pregnancy

11.3.5.1 High risk

HCPs demonstrated low knowledge with regard to how long a female patient should use effective contraception following discontinuation of Mayzent (H-Q28), as only 57% of HCPs selected the correct

answer of at least 10 days. Only 5% selected incorrect responses of fewer than 10 days, whilst 39% said “I don’t know” indicating some HCPs failed to recall this message. In clinical practice, HCPs who are discontinuing female patients from Mayzent treatment would have an opportunity to refer to the product information or educational materials, to confirm the appropriate timeframe for the use of contraception.

Patients/caregivers also demonstrated low knowledge with regard to how many days after stopping Mayzent treatment they should arrange reliable methods of birth control (P-Q18), as only 54% of patients/caregivers selected the correct answer. It is unknown how many patients were considering stopping Mayzent treatment at the time of the survey. There would be an opportunity for further information to be shared by an HCP at the point of treatment discontinuation.

It can be noted that additional materials are available for female patients of childbearing potential that reinforce the information relating to the risk of pregnancy while receiving Mayzent.

11.3.5.2 Medium/Low risk

Female patients of childbearing potential had high awareness (92%) that they must avoid getting pregnant while on Mayzent (P-Q17).

HCPs showed a good awareness (70%) of the need to discontinue treatment with Mayzent if a patient becomes pregnant (H-Q29). However, awareness of the requirement to report the pregnancy to Novartis was low (36%). Reinforcing the importance of reporting pregnancy to the MAH will ensure important safety data is reported to enhance knowledge relating to the impact of Mayzent in pregnancy.

11.4 Generalizability

Recruitment extended across 6 EU countries, covering both North and South regions, and Canada. Participating HCPs included those involved in care of relapsing MS patients who have either prescribed or been involved in the management of patients receiving Mayzent. Participating HCPs were well balanced with regards to treatment setting, including a mix of those who were hospital or office based, and variation in the size of their MS patient caseload.

Patients/caregivers reflected the MS patient population in age and gender distribution and included patients with varying MS history (time since diagnosis, previous treatments).

The participating countries provide a balance of different health care systems, and there were few significant differences between regions in EU, enabling generalizability of study results at the EU level.

12 Other information

Not applicable

13 Conclusion

The survey results confirm that an acceptable number of HCPs involved in the prescribing and management of patients receiving Mayzent recall receiving the educational materials (Prescribers checklist). A lower proportion of patients/caregivers recall receiving the educational materials from their prescribers.

Patients/caregivers who were in receipt of the educational materials were more informed on some topics than those who did not recall receiving the materials (see section 10.5.1), indicating that the materials were effective at communicating key messages. It is the responsibility of HCPs to distribute the materials

to their patients. Ensuring that patients/caregivers receive the materials will have a positive impact on knowledge levels

In summary, this robust assessment demonstrated overall appropriate understanding of the use of Mayzent, especially by HCPs. Several study limitations were acknowledged in relation to sampling considerations, response rate, survey question design, and reference to the educational materials.

The necessary information is available to HCPs and patients/caregivers in the label and patient information pack insert, in addition to being clearly explained in the educational materials. The educational materials have been thoroughly reviewed and are considered adequate to support the safe and effective use of Mayzent. With the completion of this study, the RMP commitment is fulfilled.

14 References

Not applicable

Appendices

Appendix 1 – List of protocol and protocol amendments

Document	Effective Date
Original Protocol Version 1.0 (draft)	24-Mar-2020
Protocol Version 1.2 (draft)	20-Aug-2020
Protocol Version 1.3 (draft)	04-Feb-2021
Original Protocol Version 1.4	29-Mar-2021
Protocol Version 02 (track changes)	19-May-2022
Final Protocol Version 03 (clean version)	25-Jan-2024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Appendix 4 – Patient/caregiver correct responses at multiple choice and selected single answer questions based on receipt of the educational materials

	Risk level	Answer options	Confirmed Receipt of materials	Materials not received/ unsure	*p value*
Base			**66**	**52**	
Q2. For what reasons will the doctor do a blood test before you get ready for your treatment with Mayzent (siponimod)?	Medium/low	CYP2C9 genotype	32 48%	14 27%	*p = 0.02*
		White blood cell count	29 44%	14 27%	*p = 0.06*
		Liver function	40 61%	15 29%	*p = 0.0006*
		Hepatitis Type B	12 18%	6 12%	*p = 0.32*
		Hematocrit	18 27%	7 13%	*p = 0.07*
		None of these	0 0%	0 0%	*N/A*
		I don't know/I am not sure	4 6%	20 38%	*p = 0.00001*
		All correct responses (with or without incorrect responses)	9 14%	1 2%	*p = 0.02*
Q3. If the person you are caring for needs to be vaccinated for chicken pox, for how long after the full course of vaccination must they wait to start their treatment with Mayzent (siponimod)?	Medium/low	6 months	5 8%	9 17%	*p = 0.10*
		4 months	4 6%	1 2%	*p = 0.27*
		2 months	10 15%	8 15%	*p = 0.97*
		1 month	20 30%	5 10%	*p = 0.006*
		I don't know/I am not sure	27 41%	29 56%	*p = 0.11*
		At least 1 month	39 59%	23 44%	*p = 0.11*
Q4. For which of the following reasons may your doctor request that you have an eye examination prior to starting treatment with	Medium/low	Have or have had previously visual disturbances or vision problems in the center of the eye	37 56%	19 37%	*p = 0.03*
		Have or have had previously inflammation of the eye	21 32%	10 19%	*p = 0.12*

Mayzent (siponimod)?		Have or have had previously high blood sugar levels/Diabetes	14 21%	8 15%	*p = 0.42*
		Cataract	12 18%	7 13%	*p = 0.49*
		Hypertension status	17 26%	8 15%	*p = 0.17*
		None of these	8 12%	2 4%	*p = 0.11*
		I don't know/I am not sure	10 15%	21 40%	*p = 0.002*
		All correct responses (with or without incorrect responses)	6 9%	3 6%	*p = 0.50*
Q6. When, if at all, may your doctor want to conduct a skin examination?	Medium/low	Prior to starting treatment with Mayzent (siponimod)	28 42%	11 21%	*p = 0.01*
		Every 6-12 months when receiving treatment with Mayzent (siponimod)	41 62%	15 29%	*p = 0.0003*
		Not at all	3 5%	4 8%	*p = 0.47*
		I don't know/I am not sure	7 11%	23 44%	*p = 0.00003*
		All correct responses (with or without incorrect responses)	13 20%	1 2%	*p = 0.003*
Q7. At the beginning of treatment with Mayzent (siponimod), for patients with heart problems how long will the doctor ask the person you are caring for, to stay in the clinic after taking the first dose so that their blood pressure and pulse can be monitored?	Low	Not applicable, I don't/the person I care for doesn't have heart problems	18 27%	17 33%	*p = 0.52*
		3 hours	8 17%	9 26%	*p = 0.31*
		6 hours	31 65%	12 34%	*p = 0.006*
		9 hours	6 13%	3 9%	*p = 0.57*
		I don't know/I am not sure	3 6%	11 31%	*p = 0.002*
		At least 6 hours of monitoring	37 77%	15 43%	*p = 0.001*

Q12. 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)?	High	Blurred or wavy vision	43 65%	31 60%	*p = 0.54*
		Changes in colour / colour looking faded	16 24%	9 17%	*p = 0.36*
		Loss of vision	20 30%	12 23%	*p = 0.38*
		Redness in the eye	14 21%	10 19%	*p = 0.79*
		Eye pain	15 23%	17 33%	*p = 0.23*
		None of these	1 2%	2 4%	*p = 0.42*
		I don't know/I am not sure	12 18%	15 29%	*p = 0.17*
		All correct responses (with or without incorrect responses)	7 11%	2 4%	*p = 0.30*
		One or more correct responses	48 73%	31 60%	*p = 0.13*
Q13. What are the symptoms that may mean you are experiencing an infection including brain infection?	High	Fever	38 58%	19 37%	*p = 0.02*
		Flu-like symptoms	22 33%	5 10%	*p = 0.002*
		Headache with or without stiff neck	33 50%	17 33%	*p = 0.06*
		Nausea and or confusion	38 58%	14 27%	*p = 0.0009*
		Swelling of the extremities due to accumulation of water	18 27%	7 13%	*p = 0.07*
		None of these	2 3%	2 4%	*p = 0.81*
		I don't know/I am not sure	8 12%	19 37%	*p = 0.002*
		All correct responses (with or without incorrect responses)	9 14%	1 2%	*p = 0.04*
		One or more correct responses	54 82%	31 60%	*p = 0.008*
Q14. What are the symptoms that may mean you may be	High	Unexplained nausea	18 27%	10 19%	*p = 0.31*
		Vomiting	20 30%	16 31%	*p = 0.96*

experiencing impaired liver function?		Abdominal/Stomach pain	35 53%	14 27%	*p = 0.004*
		Fatigue/Tiredness (overall feeling of tiredness or lack of energy)	32 48%	11 21%	*p = 0.002*
		Rash (a change in the color or in the texture of your skin that can cause itchiness)	22 33%	5 10%	*p = 0.002*
		Yellowing of the eyes or the skin	41 62%	18 35%	*p = 0.003*
		Dark urine	27 41%	24 46%	*p = 0.57*
		Headache	17 26%	7 13%	*p = 0.10*
		Fever	20 30%	8 15%	*p = 0.06*
		Productive cough	2 3%	1 2%	*p = 0.70*
		Blurred vision	7 11%	3 6%	*p = 0.35*
		Joint pain	13 20%	10 19%	*p = 0.95*
		None of these	1 2%	1 2%	*p = 0.86*
		I don’t know/I am not sure	6 9%	13 25%	*p = 0.02*
		All correct responses (with or without incorrect responses)	3 5%	0 0%	*p = 0.25*
		One or more correct responses	58 88%	36 69%	*p = 0.01*
Q15. Which skin conditions, if any, should be reported immediately to your doctor?	Medium	Skin nodules (e.g. shiny or pearly nodules)	37 56%	23 44%	*p = 0.20*
		Patches or open sores that do not heal within a few weeks	48 73%	22 42%	*p = 0.0008*
		Dryness	17 26%	10 19%	*p = 0.40*
		None of these	3 5%	1 2%	*p = 0.43*
		I don’t know/I am not sure	4 6%	16 31%	*p = 0.0004*

		Both correct responses (with or without other responses)	27 41%	13 25%	*p = 0.07*
		One or more correct responses	58 88%	32 62%	*p = 0.008*
Q.18 Time period to arrange reliable contraception after stopping treatment	Medium	6 Days	1 5%	2 12%	*Base sizes too small for testing*
		10 Days	13 59%	4 24%	
		12 Days	2 9%	2 12%	
		I don't know/ I am not sure	6 27%	9 53%	
		At least 10 days	15 68%	6 35%	

Appendix 5 – HCP correct responses at multiple choice and selected single answer questions based on receipt of the educational materials

	Risk level	Answer options	Confirmed receipt of materials	Materials not received/ unsure	*p-value*
Base			**186**	**34**	
Q5. Which of the following recent (i.e. within the last six months) test results should be made available prior to treatment initiation of Mayzent (siponimod)?	Low	Transaminase and bilirubin levels	140 75%	23 68%	*p = 0.35*
		Full blood count	158 85%	26 76%	*p = 0.22*
		Cholesterol	39 21%	5 15%	*p = 0.40*
		Calcium	42 23%	7 21%	*p = 0.80*
		Glucose	47 25%	5 15%	*p = 0.18*
		None of these	2 1%	0 0%	*p = 0.54*
		I don’t know/I am not sure	5 3%	2 6%	*p = 0.33*
		All correct responses (with or without incorrect responses)	121 65%	17 50%	*p = 0.08*
Q7. When, if at all, should skin examination be performed for patients treated with Mayzent (siponimod)?	Medium	Prior to treatment initiation	108 58%	21 62%	*p = 0.69*
		Every 6-12 months following initiation	141 76%	24 71%	*p = 0.52*
		Not at all	1 1%	1 3%	*p = 0.17*
		I don’t know/I am not sure	9 5%	4 12%	*p = 0.12*
		All correct responses (with or without incorrect responses)	73 39%	16 47%	*p = 0.34*
Q10. Within what time period do you need to check liver transaminases before commencing patients on Mayzent (siponimod)?	Low	2 months	55 30%	5 15%	*p = 0.07*
		3 months	56 30%	13 38%	*p = 0.35*
		6 months	67 36%	12 35%	*p = 0.94*
		12 months	0	0	*N/A*

		0%	0%	
	I don't know/I am not sure	8 4%	4 12%	*p = 0.08*
	Any time *within* 6 months	178 96%	30 88%	*p = 0.08*
Q13. The recommended maintenance dose/s for Mayzent (siponimod) after the up-titration schedule is/are: Medium	0.5 mg	1 1%	1 3%	*p = 0.17*
	1 mg	53 28%	7 21%	*p = 0.34*
	1.25 mg	13 7%	4 12%	*p = 0.34*
	2 mg	138 74%	18 53%	*p = 0.01*
	I don't know/I am not sure	14 8%	6 18%	*p = 0.06*
	All correct responses (with or without incorrect responses)	33 18%	2 6%	*p = 0.054*
Q16. For which type/s of patients is Mayzent (siponimod) not recommended? High	Patients with concomitant treatment with class Ia or class III anti-arrhythmic medications	127 68%	19 56%	*p = 0.16*
	Patients with QTC prolongation >500 msec	129 69%	20 59%	*p = 0.23*
	Patients with history of recurrent syncope	67 36%	13 38%	*p = 0.81*
	Patients with history of symptomatic bradycardia	129 69%	21 62%	*p = 0.38*
	Patients with uncontrolled hypertension	99 53%	12 35%	*p = 0.054*
	Patients with severe untreated sleep apnoea	52 29%	5 15%	*p = 0.08*
	Patients with active malignancies	128 69%	19 56%	*p = 0.14*
	Patients with controlled hypertension	13 7%	2 6%	*p = 0.81*
	Patients treated with benzodiazepines	13 7%	3 9%	*p = 0.70*

		Patients treated with beta-blockers	61 33%	10 29%	*p = 0.70*
		None of these	1 1%	1 3%	*p = 0.17*
		I don't know/I am not sure	8 4%	5 15%	*p = 0.02*
		All correct responses (with or without incorrect responses)	17 9%	4 12%	*p = 0.63*
Q17. How many hours should a patient with sinus bradycardia, 1st/2nd degree AV block or history of myocardial infarction or heart failure be monitored at treatment initiation with Mayzent (siponimod)?	Medium	3	17 9%	5 15%	*p = 0.32*
		5	16 9%	2 6%	*p = 0.59*
		6	105 56%	15 44%	*p = 0.18*
		8	19 10%	4 12%	*p = 0.79*
		I don't know/I am not sure	29 16%	8 24%	*p = 0.26*
		At least 6 hours of monitoring	124 67%	19 56%	*p = 0.23*
Q18. 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?	Medium	New onset second degree or higher AV block	139 75%	17 50%	*p = 0.004*
		QTc>500 msec	116 62%	15 44%	*p = 0.046*
		Hypotension	50 27%	7 21%	*p = 0.44*
		Transient sinus bradycardia of 50 bpm	90 48%	16 47%	*p = 0.89*
		None of these	5 3%	2 6%	*p = 0.33*
		I don't know/I am not sure	17 9%	7 21%	*p = 0.049*
		All correct responses (with or without incorrect responses)	108 58%	13 38%	*p = 0.03*
Q19. Does your center perform the first dose monitoring (FDM) for patients with CV risk or do you send your patients to other	Low	Perform first dose monitoring in my own center	138 74%	22 65%	*p = 0.25*
		Send patients to other specialised center for first dose monitoring	43 23%	8 24%	*p = 0.96*

specialized MS center for FDM?		Do not conduct first dose monitoring in patients with CV risk	5 3%	4 12%	*p = 0.01*
		All correct responses (with or without incorrect responses)	181 97%	30 88%	*p = 0.27*
Q20. For which patients due to be initiated on Mayzent (siponimod) should you conduct an ophthalmologic examination before starting treatment?	High	Diabetes mellitus	117 63%	16 47%	*p = 0.08*
		Uveitis	103 55%	17 50%	*p = 0.56*
		History of retinal disorders	116 62%	13 38%	*p = 0.009*
		Severe myopia	56 30%	8 24%	*p = 0.44*
		None of these	4 2%	2 6%	*p = 0.22*
		I don’t know/I am not sure	19 10%	10 29%	*p = 0.002*
		All correct responses (with or without incorrect responses)	67 36%	11 32%	*p = 0.68*
Q25. Following a full course of vaccination against Varicella-Zoster Virus (VZV) for how long should you delay treatment initiaton?	Low	2 weeks	8 4%	3 9%	*p = 0.27*
		1 month	100 54%	15 44%	*p = 0.30*
		2 months	18 10%	1 3%	*p = 0.20*
		3 months	31 17%	6 18%	*p = 0.89*
		I don’t know/I am not sure	29 16%	9 26%	*p = 0.12*
		At least 1 month	149 80%	22 65%	*p = 0.047*
Q28. For how long should a female patient use effective contraception following discontinuation of Mayzent (siponimod)? For at least…(days)	High	2	1 1%	0 0%	*N/A*
		3	1 1%	0 0%	*N/A*
		5	1 1%	0 0%	*N/A*
		7	4 2%	3 9%	*N/A*
		10	78 42%	11 32%	*p = 0.30*
		14	2	0	*N/A*

			1%	0%	
		15	2 1%	0 0%	*N/A*
		20	1 1%	1 3%	*N/A*
		21	1 1%	0 0%	*N/A*
		28	4 2%	0 0%	*N/A*
		30	23 12%	2 6%	*p = 0.27*
		Don't know	68 37%	17 50%	*p = 0.14*
		At least 10 days	111 60%	14 41%	*p = 0.045*
Q29. For patients who become pregnant during treatment, what is the correct approach from the options below?	Medium/low	Patient treatment should be discontinued immediately	135 73%	19 56%	*p = 0.051*
		Patient should be titrated off treatment	33 18%	5 15%	*p = 0.67*
		Pregnancy should be reported to Novartis	67 36%	12 35%	*p = 0.94*
		None of these	4 2%	2 6%	*p = 0.22*
		I don't know/I am not sure	13 7%	9 26%	*p = 0.0005*
		All correct responses (with or without incorrect responses)	53 28%	10 29%	*p = 1.00*
Q30. What should you do if a patient develops unexplained nausea, vomiting, abdominal pain and/or anorexia when receiving Mayzent (siponimod)?		Continue as nothing serious could happen	15 8%	0 0%	*p = 0.09*
		Check liver enzymes	148 80%	26 76%	*p = 0.68*
Low		Discontinue treatment if significant liver injury is confirmed	135 73%	27 79%	*p = 0.41*
		I don't know/I am not sure	4 2%	1 3%	*p = 0.78*
		All correct responses (with or without incorrect responses)	109 58%	20 59%	*p = 1.00*