



WHEN CHOOSING A TREATMENT FOR PATIENTS WITH
FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS¹

EVIDENCE AND EXPERIENCE MATTER

**MAYZENT[®] IS THE FIRST AND ONLY ORAL DMT studied
and proven to delay disability progression in a more
progressed RMS population, including active SPMS^{1,2*}**

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; RMS=relapsing multiple sclerosis; SPMS=secondary progressive MS.
*Patients in EXPAND had a mean EDSS score of 5.4.³

INDICATION

MAYZENT[®] (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindications

- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Please see additional Important Safety Information on pages 12-13 and accompanying full Prescribing Information.

IDENTIFYING APPROPRIATE PATIENTS MATTERS MAYZENT® WAS PROVEN TO DELAY DISABILITY PROGRESSION IN A MORE PROGRESSED RMS POPULATION, INCLUDING αSPMS¹

Sample patient profiles:



JESS, 41 YEARS OLD*
Science teacher

"I worry that my RMS is starting to affect my teaching."

WHAT'S CHANGED IN THE LAST YEAR

- Trouble concentrating
- Difficulty organizing lesson plans
- Mild motor deficits, such as weakness in right leg (observed slight right foot drag)

PATIENT HISTORY

- **6 YEARS** since MS diagnosis
- **RELAPSES ARE LESS FREQUENT**, but last MRI revealed 1 new GdE lesion and an increase in T2 lesion volume
- **1 TREATMENT SINCE DIAGNOSIS**
- Initiated current oral medication 2 years ago

EDSS score: **3.5**

JAMIE, 48 YEARS OLD*
Accountant

"Walking my dog is something I used to look forward to, and now that I need a cane more often, I just can't do it."

WHAT'S CHANGED IN THE LAST YEAR

- Ambulatory difficulty
 - Can no longer take dog on walks
 - Intermittent use of cane
- Moderate urinary urgency
- Chronic fatigue
- Has trouble remembering words

PATIENT HISTORY

- **13 YEARS** since MS diagnosis
- **1 RELAPSE** in the past 2 years, last MRI showed 1 new GdE lesion and slow expansion of T2 lesion volume
- **2 TREATMENTS SINCE DIAGNOSIS**
- Initiated current oral medication 2 years ago

EDSS score: **5.5**



*Not an actual patient.

αSPMS=active secondary progressive MS; GdE=gadolinium-enhancing; MRI=magnetic resonance imaging; MS=multiple sclerosis.

IMPORTANT SAFETY INFORMATION (CONT)

Infections: MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after

discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy.

Please see additional Important Safety Information on pages 12-13 and accompanying full Prescribing Information.

MECHANISM OF ACTION MATTERS DUAL MOA SELECTIVELY TARGETS S1P_{1,5}: 2 KEY RECEPTORS THOUGHT TO PLAY A ROLE IN RMS INFLAMMATION AND NEURODEGENERATION^{1,4-7}

MAYZENT is an oral, selective S1P receptor modulator for progressing patients along the RMS continuum¹

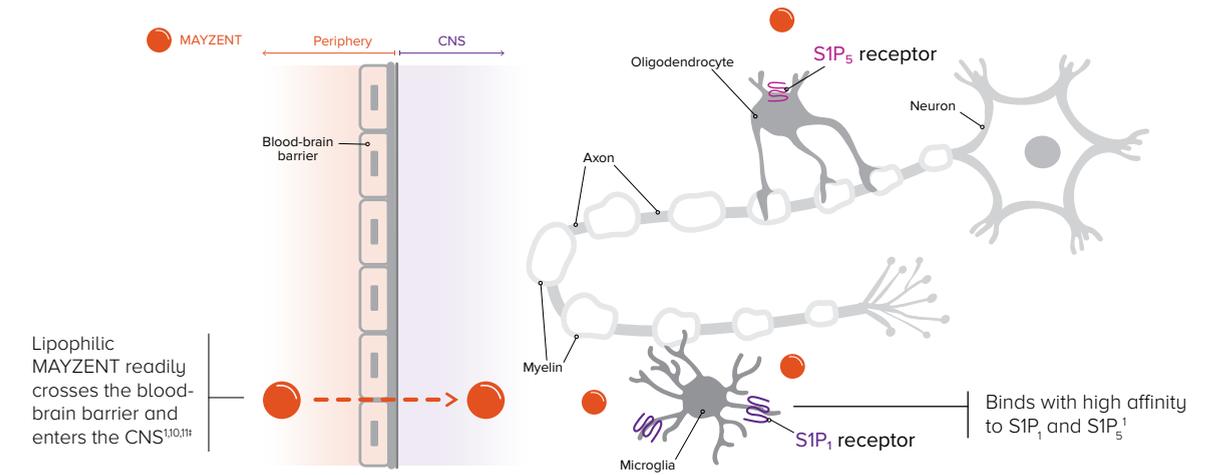
THE PROPOSED DUAL MOA OF MAYZENT

WORKS IN THE PERIPHERY to limit active lymphocytes from leaving the lymph nodes, which may reduce lymphocyte migration into the CNS.^{1,8}

- Lymphocytes are stored, not destroyed, in the lymph nodes; upon discontinuation, blood lymphocyte counts rapidly recover within 10 days^{1,8**}

WORKS CENTRALLY by crossing the blood-brain barrier into the CNS.^{1,8,9}

Based on animal studies, siponimod readily crosses the blood-brain barrier and enters the CNS.^{1,8,9}



The mechanism by which siponimod exerts therapeutic effects on MS is unknown but may involve reduction of lymphocytes in the CNS.¹

BELIEVED TO WORK IN 2 PLACES: PERIPHERY AND CNS^{1,8,9,12}

CNS=central nervous system; MOA=mechanism of action; S1P=sphingosine 1-phosphate.

¹In 90% of patients.

⁸After stopping MAYZENT treatment, residual lowering of peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose.

⁹Based on animal studies.^{1,8,9}

IMPORTANT SAFETY INFORMATION (CONT)

Infections (cont): Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected,

MAYZENT should be suspended until cryptococcal infection has been excluded.

MAYZENT®
(siponimod) tablets
0.25 mg • 2 mg

EXPERIENCE MATTERS

EXPAND STUDIED A BROAD RANGE OF DISABILITY—INCLUDING PATIENTS PREVIOUSLY TREATED WITH A DMT³

MAYZENT[®] was evaluated in *EXPAND*—the largest Phase III study of SPMS patients to date (N=1651)¹³

BASELINE PATIENT CHARACTERISTICS FOR PATIENTS ON MAYZENT³

Age (mean)	48 YEARS (Range: 21-61 years)	EDSS progression documented in the 2 years prior to study	100% of patients
Previous treatment	78% (n=860) had received a DMT	Patients with GdE lesions (%)	21% of patients
Time since onset of MS symptoms (mean)	17 YEARS	Patients with at least 1 relapse within the 2 years prior to study entry (%)	36% of patients
Time since initial MS diagnosis (mean)	13 YEARS (Range: 0-44 years)	EDSS score (mean)	5.4 (Range: 3.0-6.5)

AT THE FIRST SIGNS OF PROGRESSION IN RMS AND ACTIVE SPMS, CHOOSE MAYZENT

IMPORTANT SAFETY INFORMATION (CONT)

Infections (cont): If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine

1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported.

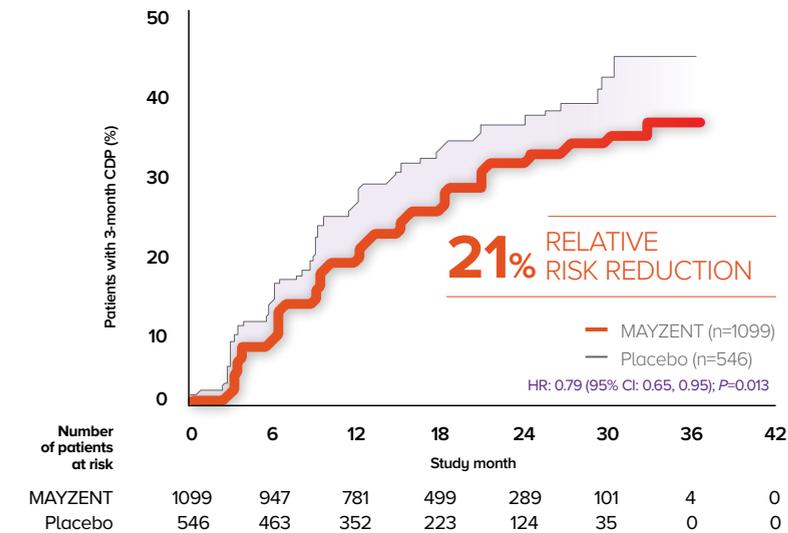
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EFFICACY MATTERS

MAYZENT[®] WAS PROVEN TO DELAY DISABILITY PROGRESSION IN THE *EXPAND* CORE STUDY³

PRIMARY END POINT RESULTS¹

TIME TO 3-MONTH CDP vs PLACEBO



- The proportion of patients with 3-month CDP for MAYZENT was 26% vs 32% for placebo³
- CDP was defined as a ≥ 1 -point increase from baseline in EDSS score (0.5-point increase for patients with a baseline EDSS score of ≥ 5.5) sustained for 3 months¹
- Although MAYZENT had a significant effect on CDP in patients with active SPMS (relapse in the 2 years prior to study entry), its effect in patients with nonactive SPMS was not statistically significant¹

KEY SECONDARY END POINT RESULTS*

T25-FW TEST

Time to 3-month confirmed deterioration by $\geq 20\%$ on the T25-FW test was not statistically significant vs placebo ($P=NS$)¹

CNS TISSUE MEASURE: T2 LESION VOLUME

Reduced the expansion of T2 lesion volume at 12 and 24 months vs placebo (adjusted mean; $P<0.01$)¹

- Change from baseline in T2 lesion volume: 184 mm³ for patients on MAYZENT vs 879 mm³ for placebo¹

*Nominal P value, not corrected for multiple comparisons.

*In *EXPAND*, a prespecified hierarchical analysis consisted of the primary end point and these 2 key secondary end points. The T25-FW test key end point was not significant; therefore, the T2 lesion volume key secondary end point was considered nominal. The remaining end points were not corrected for multiple comparisons.^{1,3}

CDP=confirmed disability progression; CI=confidence interval; HR=hazard ratio; NS=not significant; T25-FW=timed 25-foot walk.

IMPORTANT SAFETY INFORMATION (CONT)

Infections (cont): Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

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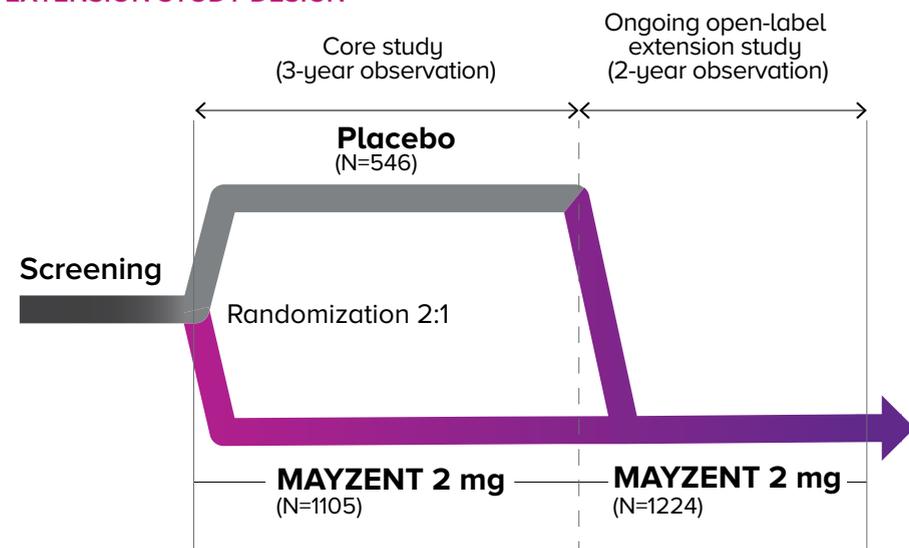
CLINICAL EXPERIENCE MATTERS INTERIM ANALYSIS OF EXPLORATORY DATA UP TO 5 YEARS¹⁴

EXPAND OPEN-LABEL EXTENSION STUDY INTERIM EXPLORATORY DATA¹⁴

The objective of the study is to evaluate the long-term safety and tolerability of MAYZENT®. The extension study allows patients who completed the core part of the EXPAND study to continue with MAYZENT, and aims to provide long-term safety data, as well as evaluate exploratory long-term data on efficacy measures.

Of the 1224 patients who entered into the extension study from the core study, 593 (72.2%) of MAYZENT patients (continuous MAYZENT group) and 285 (71.4%) of placebo patients (placebo-switch group) continued into the extension. The mean exposure to MAYZENT for all patients (core + extension) was 39.4 months. 18.5% of all study patients (core + extension) reached the 5-year MAYZENT treatment milestone at the time of this analysis.

OPEN-LABEL EXTENSION STUDY DESIGN¹⁴



The extension study end points differ from the core study and were predefined as exploratory in the extension protocol.^{15*}

*SDMT was assessed but was not an exploratory end point in the extension study. Additional long-term data that was collected but not listed: 6-month confirmed worsening of at least 20% from baseline in the T25-FW test, MRI parameters, Multiple Sclerosis Walking Scale-12, and EuroQoL.^{14,15}
SDMT=Symbol Digit Modalities Test.

IMPORTANT SAFETY INFORMATION (CONT)

Infections (cont): Caution should be used when combining treatment (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk.

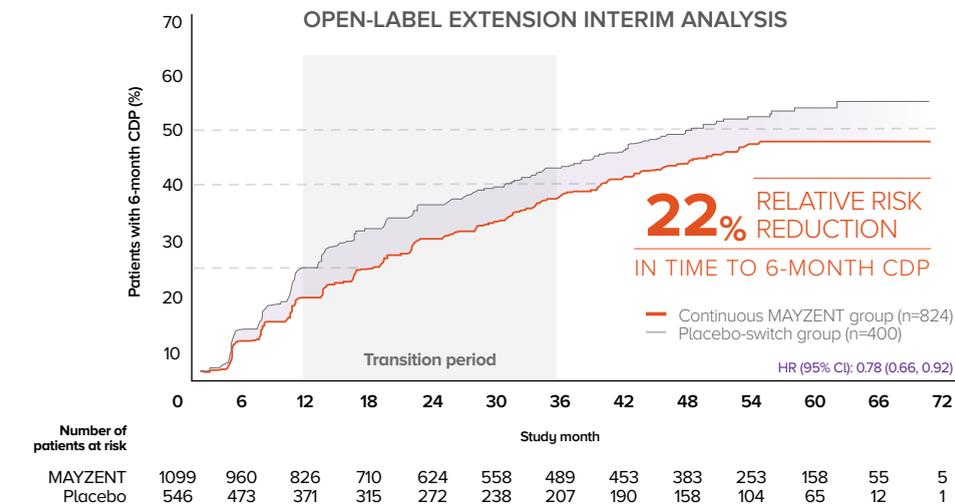
Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

Please see additional Important Safety Information on pages 12-13 and accompanying full Prescribing Information.

LONG-TERM DATA MATTERS SELECT EFFICACY ASSESSMENTS UP TO 5 YEARS WERE CONSISTENT WITH THE CORE STUDY^{3,14†}

SELECT LONG-TERM EXPLORATORY END POINTS AND ASSESSMENTS

TIME TO 6-MONTH CDP



- In this analysis, patients who started in the MAYZENT treatment arm experienced a greater reduction in the risk of disability progression vs patients who switched to MAYZENT later¹⁴
- The extension study end points differ from the core study and were predefined as exploratory in the extension protocol¹⁵
- SDMT was assessed but was not an exploratory end point in the extension study. Additional long-term data that were collected but not listed: 6-month confirmed worsening of at least 20% from baseline in the T25-FW test, MRI parameters, Multiple Sclerosis Walking Scale-12, and EuroQoL.^{14,15}

ANNUALIZED RELAPSE RATE

52% RELATIVE REDUCTION in ARR vs placebo-switch group

- Defined as the average number of confirmed relapses per year (0.051 for continuous MAYZENT vs 0.106 for placebo-switch group)¹⁴

COGNITIVE PROCESSING SPEED

23% OVERALL REDUCTION in the risk of decrease in SDMT score vs placebo-switch group

- SDMT was the only cognitive assessment conducted in the extension study¹⁴

These exploratory analyses represent chance findings. No conclusions of statistical or clinical significance can be drawn. Consider interim analysis open-label extension study limitations when interpreting data. The open-label extension study is not blinded, not controlled, and includes inherent self-selection bias for remaining in the trial.

ARR=annualized relapse rate.

[†]6-month CDP, ARR, and SDMT were exploratory end points and assessments of efficacy measurements, respectively, in the EXPAND extension study.¹⁵

IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction

Delays: Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization



EXPERIENCE MATTERS DEMONSTRATED SAFETY PROFILE IN THE EXPAND CORE STUDY¹

Adverse events that occurred in $\geq 5\%$ of patients taking MAYZENT[®] and at a rate $\geq 1\%$ higher than in patients receiving placebo

PROPORTION OF PATIENTS WITH ADVERSE EVENTS

	MAYZENT 2 mg (n=1099)	Placebo (n=546)
Headache	15%	14%
Hypertension	13%	9%
Transaminase levels increased	11%	3%
Falls	11%	10%
Peripheral edema	8%	4%
Nausea	7%	4%
Dizziness	7%	5%
Diarrhea	6%	4%
Bradycardia	6%	3%
Pain in extremity	6%	4%

In the core study, the most common adverse events (incidence $\geq 10\%$) were headache (15%), hypertension (13%), and transaminase increases (11%).

Treatment discontinuation rates due to adverse events were similar across treatment arms.

- 8.5% of patients taking MAYZENT discontinued treatment due to adverse events vs 5.1% with placebo

WITH MAYZENT, lymphocytes are stored, not destroyed, in the lymph nodes. The half-life of MAYZENT is approximately 30 hours, and upon discontinuation, blood lymphocyte counts rapidly recover within 10 days*†

The mechanism by which siponimod exerts therapeutic effects on MS is unknown but may involve reduction of lymphocytes in the CNS.

*In 90% of patients.

†After stopping MAYZENT treatment, residual lowering of peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose.

IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction Delays (cont):

MAYZENT was not studied in patients who had (cont):

- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus

syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker

- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

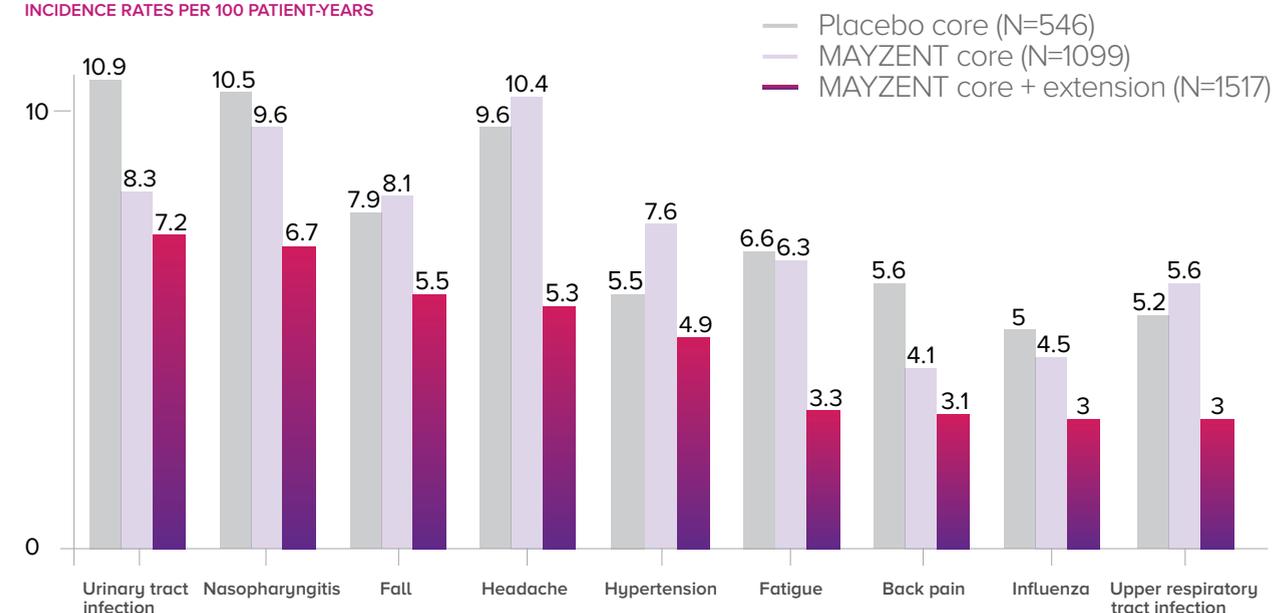
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EXPERIENCE MATTERS THE SAFETY PROFILE OF MAYZENT REMAINED CONSISTENT WITH THE CORE STUDY UP TO 5 YEARS¹⁴

Adverse events that occurred in $\geq 3\%$ of patients taking MAYZENT in the core and extension studies (analysis results were consistent with core study per listed criteria)

PROPORTION OF PATIENTS WITH ADVERSE EVENTS

INCIDENCE RATES PER 100 PATIENT-YEARS



IMPORTANT SAFETY INFORMATION (CONT)

Bradyarrhythmia and Atrioventricular Conduction Delays (cont):

Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥ 4 consecutive daily doses are missed.

Respiratory Effects: MAYZENT may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy if clinically warranted.

Liver Injury: Elevation of transaminases may occur in

patients taking MAYZENT. Before starting treatment, obtain liver transaminase and bilirubin levels. Closely monitor patients with severe hepatic impairment. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked, and MAYZENT should be discontinued if significant liver injury is confirmed.

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DOSING MATTERS

INITIATING TREATMENT WITH MAYZENT® — A ONCE-DAILY ORAL¹

MAYZENT is an S1P receptor modulator with precisely determined dosing to fit your patient's distinct metabolism, as well as a tailored titration schedule to help patients safely reach their appropriate maintenance dose.¹



CONSIDERATIONS FOR INITIATION

- Genotype testing:** Patients undergo a genotype test to identify their specific variant of CYP2C9, the principal enzyme that metabolizes MAYZENT.* This genotype test identifies the appropriate MAYZENT maintenance dose.¹
- Most patients won't require an FDO during initiation:** An FDO is required only for patients with certain preexisting cardiac conditions.^{1,16}
- Titration schedule:** Initiation of MAYZENT treatment results in a transient decrease in heart rate and atrioventricular conduction delays. For all patients, a dose titration is recommended for initiation of MAYZENT treatment to help patients safely reach their maintenance dose.¹

FDO=first-dose observation.

*Patients with a CYP2C9*3/*3 genotype should not be treated with MAYZENT.¹

IMPORTANT SAFETY INFORMATION (CONT)

Cutaneous Malignancies: Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-phototherapy is not recommended.

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PATIENT ACCESS MATTERS

DEDICATED SUPPORT FOR PATIENTS PRESCRIBED MAYZENT



Our goal is to get your patients started seamlessly in just 2 steps



STEP 1: ASSESSMENTS

Take care of all baseline assessments in just one or two visits^{††}



STEP 2: TREATMENT INITIATION

Start and help patients stay on track on treatment[§]

ADDITIONAL PATIENT SUPPORT



Access & financial support options, as well as additional tools, resources, and services to help patients stay on track.



Going directly through a specialty pharmacy? Patients can enroll at start.mayzent.com for help with treatment initiation, ongoing one-on-one assistance from dedicated Coordinators, and access and reimbursement support.

ESTABLISHED PAYER COVERAGE FOR MAYZENT

- MAYZENT provides broad managed care coverage with >85% approval rates** across commercial and government insurance segments.¹⁷
- Strong access for commercially insured patients**
 - If coverage is denied, our **Bridge Program can cover medication costs** while coverage is pursued for up to **1 year**[¶]
 - \$0 copay**[¶]

[†]Bloodwork: Complete blood count, liver function tests (transaminases & bilirubin), varicella antibody titers, CYP2C9 genotype.

^{††}Medical exams: Macular edema screening, electrocardiogram (ECG).

[§]For eligible patients and commercially insured patients.

[§]Once appropriate maintenance dose has been determined based on genotype results.

[¶]Eligible patients must have commercial insurance and a valid prescription for MAYZENT. By participating, patient acknowledges intent to pursue insurance coverage for MAYZENT with their health care provider. Program requires the submission of a request for coverage within 9 months post-Program initiation in order to remain eligible. Patients will receive their maintenance drug supply each month for up to 12 months or until they receive insurance coverage approval, whichever occurs earlier. Program is not available to patients who are uninsured or whose medications are reimbursed in whole or in part by Medicare, Medicaid, TRICARE, or any other federal or state program, or where prohibited by law. Patients may be asked to re-verify insurance coverage status during the course of the Program. No purchase necessary. Program is not health insurance, nor is participation a guarantee of insurance coverage. Other limitations may apply. Novartis reserves the right to rescind, revoke, or amend the Program and discontinue support at any time without notice.

[¶]Limitations apply. Up to an \$18,000 annual limit. Offer not valid under Medicare, Medicaid, or any other federal or state program. Novartis reserves the right to rescind, revoke, or amend this Program without notice. See complete Terms & Conditions for details at www.mayzent.com.

IMPORTANT SAFETY INFORMATION (CONT)

Increased Blood Pressure: Increase in systolic and diastolic pressure was observed about 1 month after initiation of treatment and persisted with continued treatment. During therapy, blood pressure should be monitored and managed appropriately.

potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT therapy.

Fetal Risk: Based on animal studies, MAYZENT may cause fetal harm. Women of childbearing



INDICATION

MAYZENT® (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindications

- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Infections: MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected, MAYZENT should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

Caution should be used when combining treatment (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

Bradycardia and Atrioventricular Conduction Delays: Prior to initiation of MAYZENT, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker

- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥ 4 consecutive daily doses are missed.

Respiratory Effects: MAYZENT may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy if clinically warranted.

Liver Injury: Elevation of transaminases may occur in patients taking MAYZENT. Before starting treatment, obtain liver transaminase and bilirubin levels. Closely monitor patients with severe hepatic impairment. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked, and MAYZENT should be discontinued if significant liver injury is confirmed.

Cutaneous Malignancies: Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended. Monitor for suspicious skin lesions and promptly evaluate any that are observed. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended.

Increased Blood Pressure: Increase in systolic and diastolic pressure was observed about 1 month after initiation of treatment and persisted with continued treatment. During therapy, blood pressure should be monitored and managed appropriately.

Fetal Risk: Based on animal studies, MAYZENT may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, MAYZENT should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Treatment or After Stopping MAYZENT: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended.

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

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. However, residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore, caution should be applied 3-4 weeks after the last dose of MAYZENT.

Severe Increase in Disability After Stopping MAYZENT: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of an S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment, thus patients should be monitored upon discontinuation.

Most Common Adverse Reactions: Most common adverse reactions (>10%) are headache, hypertension, and transaminase increases.

Please see accompanying full Prescribing Information, including Medication Guide.



FOR PATIENTS WITH FIRST SIGNS OF PROGRESSION IN
RMS AND ACTIVE SPMS¹

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Visit: mayzenthcp.com

**STAY AHEAD OF PROGRESSION—
CHOOSE MAYZENT[®]1**

**DUAL
ACTION.**



SIP₁ SIP₅

DUAL MOA SELECTIVELY

TARGETS SIP_{1,5}: 2 key receptors thought
to play a role in RMS inflammation
and neurodegeneration¹⁴⁻⁷

THE PROPOSED MOA OF MAYZENT



WORKS IN THE PERIPHERY by limiting
active lymphocytes from leaving the lymph nodes,
which may reduce lymphocyte migration into the CNS¹⁸



WORKS CENTRALLY by crossing the
blood-brain barrier into the CNS^{18,9†}
**The mechanism by which siponimod exerts
therapeutic effects on MS is unknown.¹**

**DELAY
PROGRESSION.**



FIRST AND ONLY ORAL DMT studied and proven to
delay disability progression in a more progressed RMS population,
including active SPMS^{12*}

■ Disability progression was measured by the EDSS, which
includes combined physical and cognitive functions, with
significance in time to 3-month CDP in aSPMS^{3,8}



DEMONSTRATED SAFETY PROFILE in the
largest trial designed for this more progressed patient
population in RMS¹³



**SELECT INTERIM ASSESSMENTS UP TO
5 YEARS WERE CONSISTENT** with the EXPAND
core study, and patients who started in the MAYZENT treatment
arm experienced a greater reduction in the risk of disability
progression vs patients who switched to MAYZENT later^{3,14†}

*Patients in EXPAND had a mean EDSS score of 5.4.³

†Based on animal studies.^{18,9}

‡6-month CDP, ARR, and SDMT were exploratory end points and assessments of efficacy measurements, respectively, in the EXPAND extension study.¹⁵

INDICATION

MAYZENT[®] (siponimod) is indicated for the treatment
of relapsing forms of multiple sclerosis (MS), to include
clinically isolated syndrome, relapsing-remitting
disease, and active secondary progressive disease,
in adults.

IMPORTANT SAFETY INFORMATION

Contraindications

- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

References: **1.** Mayzent [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; January 2021. **2.** Data on file. First and only progressing RMS treatment. Novartis Pharmaceuticals Corp; January 2020. **3.** Kappos L, Bar-Or A, Cree BAC, et al; for the EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263-1273. **4.** O'Sullivan C, Schubart A, Mir AK, Dev KK. The dual SIP1/SIP5 drug BAF312 (siponimod) attenuates demyelination in organotypic slice cultures. *J Neuroinflammation*. 2016;13:31. **5.** Gergely P, Nüeslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol*. 2012;167(5):1035-1037. **6.** Mannioui A, Vauzanges Q, Fini JB, et al. The Xenopus tadpole: an in vivo model to screen drugs favoring remyelination. *Mult Scler*. 2018;24(11):1421-1432. **7.** Choi JW, Chun J. Lysophospholipids and their receptors in the central nervous system. *Biochim Biophys Acta*. 2013;1831(1):20-32. **8.** Gentile A, Musella A, Bullitta S, et al. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. *J Neuroinflammation*. 2016;13(1):207. **9.** Bigaud M, Rudolph B, Briard E, Beerli C, Schubart A, Gardin A. Siponimod penetrates, distributes and acts on the central nervous system: translational insights. *Neurology*. 2020;94(suppl 15):3973. American Academy of Neurology abstract 3973. **10.** Briard E, Rudolph B, Desrivaud S, Krauser JA, Auberson YP. MS565: A SPECT Tracer for Evaluating the Brain Penetration of BAF312 (Siponimod). *ChemMedChem*. 2015;10(6):1008-1018. **11.** Behrangi N, Fischbach F, Kipp M. Mechanism of siponimod: anti-inflammatory and neuroprotective mode of action. *Cells*. 2019;8(24):1-11. **12.** Data on file. Dual mode of action of siponimod in secondary progressive multiple sclerosis: a hypothesis based on the relevance of pharmacological properties. Novartis Pharmaceuticals Corp; September 2020. **13.** Data on file. US National Library of Medicine. ClinicalTrials.gov. SPMS Clinical Trial Search Results. Accessed December 19, 2020. **14.** Data on file. Long-term efficacy and safety of Siponimod in patients with SPMS: EXPAND extension analysis up to 5 years. Novartis Pharmaceuticals Corp; May 2020. **15.** Data on file. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312. Novartis Pharmaceuticals Corp; July 2020. **16.** Data on file. Mayzent FDO analysis. Novartis Pharmaceuticals Corp; 2020. **17.** Data on file. Mayzent approval rate analysis. Novartis Pharmaceuticals Corp; June 2020. **18.** Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.

Please see additional Important Safety Information on pages 12-13 and accompanying full Prescribing Information.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAYZENT safely and effectively. See full prescribing information for MAYZENT.

MAYZENT® (siponimod) tablets, for oral use

Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Warnings and Precautions, Cutaneous Malignancies (5.6) 1/2021

INDICATIONS AND USAGE

MAYZENT is a sphingosine 1-phosphate (S1P) receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

DOSAGE AND ADMINISTRATION

- Assessments are required prior to initiating MAYZENT. (2.1)
- Titration is required for treatment initiation. (2.2, 2.3)
- The recommended maintenance dosage is 2 mg. (2.2)
- The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. (2.3)
- Administer tablets whole; do not split, crush, or chew. (2.2, 2.3)
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.25 mg and 2 mg (3)

CONTRAINDICATIONS

- Patients with a CYP2C9*3/*3 genotype. (4)
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure. (4)
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker. (4)

WARNINGS AND PRECAUTIONS

- **Infections:** MAYZENT may increase the risk. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment. Do not start in patients with active infection. (5.1)

- **Macular Edema:** An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking MAYZENT. Diabetes mellitus and uveitis increase the risk. (5.2)
- **Bradyarrhythmia and Atrioventricular Conduction Delays:** MAYZENT may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. (5.3, 7.2, 7.3)
- **Respiratory Effects:** May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. (5.4)
- **Liver Injury:** Obtain liver enzyme results before initiation. Closely monitor patients with severe hepatic impairment. Discontinue if significant liver injury occurs. (5.5)
- **Cutaneous Malignancies:** Periodic skin examination is recommended. (5.6)
- **Increased Blood Pressure:** Monitor blood pressure (BP) during treatment. (5.7)
- **Fetal Risk:** Women of childbearing potential should use effective contraception during and for 10 days after stopping MAYZENT. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence greater than 10%) are headache, hypertension, and transaminase increases. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Vaccination:** Avoid live attenuated vaccines during and for up to 4 weeks after treatment with MAYZENT. (7.4)
- **CYP2C9 and CYP3A4 Inhibitors:** Increase in siponimod exposure; concomitant use of MAYZENT with moderate CYP2C9 and moderate or strong CYP3A4 inhibitors is not recommended. (7.5)
- **CYP2C9 and CYP3A4 Inducers:** Decrease in siponimod exposure; concomitant use of MAYZENT with moderate CYP2C9 and strong CYP3A4 inducers is not recommended. (7.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2021

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MAYZENT is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of MAYZENT

Before initiation of treatment with MAYZENT, assess the following:

CYP2C9 Genotype Determination

Test patients for CYP2C9 variants to determine CYP2C9 genotype [see *Dosage and Administration* (2.2, 2.3), *Contraindications* (4), and *Use in Specific Populations* (8.6)]. An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.

Complete Blood Count

Review results of a recent complete blood count (CBC) [see *Warnings and Precautions* (5.1)].

Ophthalmic Evaluation

Obtain an evaluation of the fundus, including the macula [see *Warnings and Precautions* (5.2)].

Cardiac Evaluation

Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist and first-dose monitoring is recommended [see *Dosage and Administration* (2.4) and *Warnings and Precautions* (5.3)].

Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction [see *Drug Interactions* (7.2, 7.3)].

Current or Prior Medications

If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with MAYZENT [see *Warnings and Precautions* (5.1) and *Drug Interactions* (7.1)].

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating MAYZENT; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with MAYZENT [see *Warnings and Precautions* (5.1)].

Liver Function Tests

Obtain recent (i.e., within last 6 months) transaminase and bilirubin levels [see *Warnings and Precautions* (5.5)].

2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2

Maintenance Dosage

After treatment titration (see *Treatment Initiation*), the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 6. Dosage adjustment is required in patients with a CYP2C9*1/*3 or *2/*3 genotype [see *Dosage and Administration* (2.3)].

Administer tablets whole; do not split, crush, or chew MAYZENT tablets.

Treatment Initiation

Initiate MAYZENT with a 5-day titration, as shown in Table 1 [see *Warnings and Precautions* (5.3)]. A starter pack should be used for patients who will be titrated to the 2-mg maintenance dosage [see *How Supplied/Storage and Handling* (16.1, 16.2)].

Table 1 Dose Titration Regimen to Reach MAYZENT 2 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg
Day 5	1.25 mg	5 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3

Maintenance Dosage

In patients with a CYP2C9*1/*3 or *2/*3 genotype, after treatment titration (*see Treatment Initiation*), the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5.

Administer tablets whole; do not split, crush, or chew MAYZENT tablets.

Treatment Initiation

Initiate MAYZENT with a 4-day titration, as shown in Table 2 [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)*]. Do not use the starter pack for patients who will be titrated to the 1-mg maintenance dosage.

Table 2 Dose Titration Regimen to Reach MAYZENT 1 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

2.4 First Dose Monitoring in Patients With Certain Preexisting Cardiac Conditions

Because initiation of MAYZENT treatment results in a decrease in heart rate (HR), first-dose 6-hour monitoring is recommended for patients with sinus bradycardia [HR less than 55 beats per minute (bpm)], first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure [*see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.2)*].

First Dose 6-Hour Monitoring

Administer the first dose of MAYZENT in a setting where resources to appropriately manage symptomatic bradycardia are available. Monitor patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain an ECG in these patients at the end of the Day 1 observation period.

Additional Monitoring After 6-Hour Monitoring

If any of the following abnormalities are present after 6 hours (even in the absence of symptoms), continue monitoring until the abnormality resolves:

- The heart rate 6 hours postdose is less than 45 bpm
- The heart rate 6 hours postdose is at the lowest value postdose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 6 hours postdose shows new onset second-degree or higher AV block

If post-dose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or if ECG 6 hours post-dose shows new onset second-degree or higher AV block or QTc greater than or equal to 500 msec, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 6-hour monitoring after the second dose.

Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy (which may include overnight monitoring) during treatment initiation, if treatment with MAYZENT is considered in patients:

- With some preexisting heart and cerebrovascular conditions [see *Warnings and Precautions* (5.3)]
- With a prolonged QTc interval before dosing or during the 6-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes [see *Warnings and Precautions* (5.3) and *Drug Interactions* (7.2)]
- Receiving concurrent therapy with drugs that slow heart rate or AV conduction [see *Drug Interactions* (7.2, 7.3)]

2.5 Reinitiation of MAYZENT After Treatment Interruption

After the initial titration is complete, if MAYZENT treatment is interrupted for 4 or more consecutive daily doses, reinitiate treatment with Day 1 of the titration regimen [see *Dosage and Administration* (2.2, 2.3)]; also complete first-dose monitoring in patients for whom it is recommended [see *Dosage and Administration* (2.4)].

3 DOSAGE FORMS AND STRENGTHS

0.25 mg tablet: Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'T' on other side.

2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'II' on other side.

4 CONTRAINDICATIONS

MAYZENT is contraindicated in patients who have:

- A CYP2C9*3/*3 genotype [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.5)]
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker [see *Warnings and Precautions* (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

MAYZENT causes a dose-dependent reduction in peripheral lymphocyte count to 20% to 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections, some serious in nature [see *Clinical Pharmacology* (12.2)]. Life-threatening and rare fatal infections have occurred in association with MAYZENT.

In Study 1 [see *Clinical Studies* (14)], the overall rate of infections was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent CBC (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period [see *Warnings and Precautions* (5.12)].

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Cryptococcal Infections

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians

should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections

Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the rate of herpetic infections was 4.6% in MAYZENT-treated patients compared to 3.0% of patients receiving placebo. In Study 2, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT (*see Vaccinations below*).

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with an S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with MAYZENT should be suspended until PML has been excluded.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy [*see Drug Interactions (7.1)*].

Vaccinations

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT, following which initiation of treatment with MAYZENT should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment [*see Drug Interactions (7.1)*].

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema

Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the

examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.3 Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of MAYZENT treatment results in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of MAYZENT [see *Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2)*].

MAYZENT was not studied in patients who had:

- In the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV-block or higher grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see *Drug Interactions (7.2)*]

Reduction in Heart Rate

After the first titration dose of MAYZENT, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3-4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days, with maximal decrease from Day 1-baseline reached on Day 5-6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5-6 bpm. Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention [see *Adverse Reactions (6.1)*]. Heart rates below 40 bpm were rarely observed.

Atrioventricular Conduction Delays

Initiation of MAYZENT treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested in most of the cases as first-degree AV block (prolonged PR interval on ECG), which occurred in 5.1% of MAYZENT-treated patients and in 1.9% of patients receiving placebo in Study 1. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at the time of treatment initiation with MAYZENT in less than 1.7% of patients in clinical trials. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, rarely required treatment with atropine, and did not require discontinuation of MAYZENT treatment.

If treatment with MAYZENT is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec)
- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see *Drug Interactions (7.2)*]
- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block [see *Contraindications (4)*]

Treatment-Initiation Recommendations

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects [see *Dosage and Administration (2.2, 2.3)*].

- In patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure, if not contraindicated, ECG testing and first-dose monitoring is recommended [see *Dosage and Administration (2.1, 2.4) and Contraindications (4)*].
- Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.
- Use of MAYZENT in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.
- Experience with MAYZENT is limited in patients receiving concurrent therapy with drugs that decrease heart rate (e.g., beta-blockers, calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate, such as ivabradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.
 - For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing MAYZENT treatment. If the resting heart rate is greater than 50 bpm under chronic beta-blocker treatment, MAYZENT can be introduced. If resting heart rate is less than or equal to 50 bpm, beta-blocker treatment should be interrupted until the baseline heart rate is greater than 50 bpm. Treatment with MAYZENT can then be initiated and treatment with a beta-blocker can be reinitiated after MAYZENT has been up-titrated to the target maintenance dosage [see *Drug Interactions (7.3)*].
 - For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate [see *Dosage and Administration (2.4) and Drug Interactions (7.2)*].

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

If a titration dose is missed, or if 4 or more consecutive daily doses are missed during maintenance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommendations [see *Dosage and Administration (2.2, 2.3)*].

5.4 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV₁) were observed in MAYZENT-treated patients as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV₁ from baseline compared to placebo was 88 mL [95% confidence interval (CI): 139, 37] at 2 years. The mean difference between MAYZENT-treated patients and patients receiving placebo in percent predicted FEV₁ at 2 years was 2.8% (95% CI: -4.5, -1.0). There is insufficient information to determine the reversibility of the decrease in FEV₁ after drug discontinuation. In Study 1, five patients discontinued MAYZENT because of decreases in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV₁ were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

5.5 Liver Injury

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of MAYZENT therapy.

In Study 1, elevations in transaminases and bilirubin were observed in 10.1% of MAYZENT-treated patients compared to 3.7% of patients receiving placebo, mainly because of transaminase [alanine aminotransferase/aspartate aminotransferase/gamma-glutamyltransferase (ALT/AST/GGT)] elevations.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of MAYZENT. In clinical trials, MAYZENT was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should have liver enzymes checked. MAYZENT should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

5.6 Cutaneous Malignancies

Long-term use of S1P modulators, including MAYZENT, have been associated with an increased risk of basal cell carcinoma (BCC). In Study 1, the incidence of BCC was 1.0% in MAYZENT-treated patients. Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with MAYZENT and in patients treated with another S1P modulator.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended in patients taking MAYZENT.

5.7 Increased Blood Pressure

In Study 1, MAYZENT-treated patients had an average increase over placebo of approximately 3 mmHg in systolic pressure and 1.2 mmHg in diastolic pressure, which was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertension was reported as an adverse reaction in 12.5% of MAYZENT-treated patients and in 9.2% of patients receiving placebo. Blood pressure should be monitored during treatment with MAYZENT and managed appropriately.

5.8 Fetal Risk

Based on animal studies, MAYZENT may cause fetal harm [*see Use in Specific Populations (8.1)*]. Because it takes approximately 10 days to eliminate MAYZENT from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT treatment.

5.9 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an S1P receptor modulator. Such events have not been reported for MAYZENT-treated patients in the development program. However, should a MAYZENT-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, MAYZENT should be discontinued.

5.10 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended [*see Drug Interactions (7.1)*].

5.11 Severe Increase in Disability After Stopping MAYZENT

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of an S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.12 Immune System Effects After Stopping MAYZENT

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

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy [*see Clinical Pharmacology (12.2)*]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte

count, may persist for up to 3 to 4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 3 to 4 weeks after the last dose of MAYZENT [see *Drug Interactions (7.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Infections [see *Warnings and Precautions (5.1)*]
- Macular Edema [see *Warnings and Precautions (5.2)*]
- Bradyarrhythmia and Atrioventricular Conduction Delays [see *Warnings and Precautions (5.3)*]
- Respiratory Effects [see *Warnings and Precautions (5.4)*]
- Liver Injury [see *Warnings and Precautions (5.5)*]
- Cutaneous Malignancies [see *Warnings and Precautions (5.6)*]
- Increased Blood Pressure [see *Warnings and Precautions (5.7)*]
- Fetal Risk [see *Warnings and Precautions (5.8)*]
- Posterior Reversible Encephalopathy Syndrome [see *Warnings and Precautions (5.9)*]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies [see *Warnings and Precautions (5.10)*]
- Severe Increase in Disability After Stopping MAYZENT [see *Warnings and Precautions (5.11)*]
- Immune System Effects After Stopping MAYZENT [see *Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 [see *Clinical Studies (14)*] and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.

Table 3 Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)

Adverse Reaction	MAYZENT 2 mg (N = 1099) %	Placebo (N = 546) %
Headache ^a	15	14
Hypertension ^b	13	9
Transaminase increased ^c	11	3
Falls	11	10
Edema peripheral ^d	8	4
Nausea	7	4
Dizziness	7	5
Diarrhea	6	4
Bradycardia ^e	6	3
Pain in extremity ^f	6	4

Terms were combined as follows:

^aheadache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.

^bhypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.

^calanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.

^dedema peripheral, joint swelling, fluid retention, swelling face.

^ebradycardia, sinus bradycardia, heart rate decreased.

^fpain in extremity and limb discomfort.

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), asthenia, and pulmonary function test decreased [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)*].

Seizures

In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV₁) were observed in patients treated with MAYZENT [*see Warnings and Precautions (5.4)*].

Vascular Events

Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Malignancies

Malignancies such as basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and seminoma were reported in MAYZENT-treated patients in Study 1 (in the core or extension parts). The risk of basal cell carcinoma is increased in MAYZENT-treated patients, and an increased risk of cutaneous malignancies has also been reported in association with another S1P modulator [*see Warnings and Precautions (5.6)*].

7 DRUG INTERACTIONS

7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration [*see Warnings and Precautions (5.1)*].

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects [*see Warnings and Precautions (5.10)*].

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended.

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

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate

MAYZENT has not been studied in patients taking QT prolonging drugs.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) [*see Warnings and Precautions (5.3) and Drug Interactions (7.3)*]. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers

Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT [*see Warnings and Precautions (5.3)*]. Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT [*see Clinical Pharmacology (12.2)*].

7.4 Vaccination

During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination [*see Warnings and Precautions (5.1)*].

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT [*see Warnings and Precautions (5.1)*].

7.5 CYP2C9 and CYP3A4 Inhibitors

Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYP2C9 and CYP3A4 Inducers

Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and *2/*3 genotype [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman (*see Data*). Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss

and fetal abnormalities (external, urogenital, and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post-implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 2 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryoletality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less than that in humans at the RHD.

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturation were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m² basis.

8.2 Lactation

Risk Summary

There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT [see *Use in Specific Populations (8.1)*]. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period [see *Warnings and Precautions (5.8)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Oral administration of siponimod (0, 5, 15, or 50 mg/kg/day) to young rats from postnatal day 25 to 70 resulted in mortality, lung histopathology (alveolar/interstitial edema, fibrin, interstitial mixed cell infiltration) and decrease in body weight gain at the mid and high doses. Neurobehavioral impairment (decreased acoustic startle response) was observed at the high dose but was reversible by the end of the recovery period. Decrease in immune function (T-cell dependent antibody response) was observed at all doses and had not fully recovered by 4 weeks after the end of dosing. A no-effect dose for adverse effects in juvenile animals was not identified.

8.5 Geriatric Use

Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYP2C9 Genotype

Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4% to 0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.5)*].

10 OVERDOSAGE

In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed [see *Warnings and Precautions (5.3, 5.7) and Clinical Pharmacology (12.2)*].

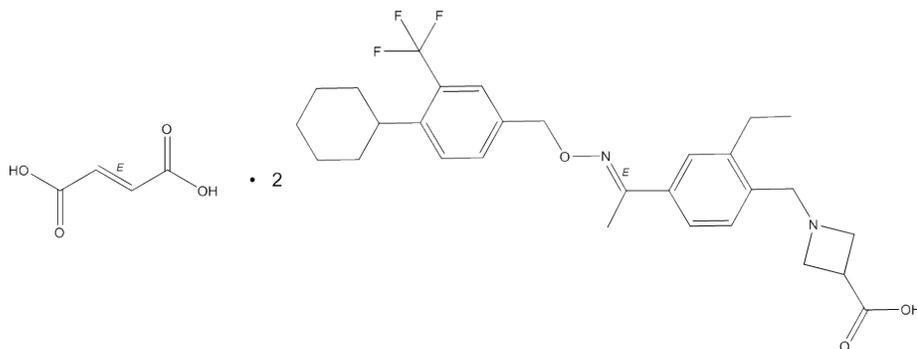
There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

11 DESCRIPTION

MAYZENT tablets contains siponimod, an S1P receptor modulator, as 2:1 co-crystal of siponimod and fumaric acid and has the following chemical name:

1-[[4-[(1E)-1-[[[4-Cyclohexyl-3-(trifluoromethyl)phenyl]methoxy]imino]ethyl]-2-ethylphenyl]methyl]-3-azetidincarboxylic acid (2E)-2-butenedioate (2:1). Its molecular formula is $C_4H_4O_4 \cdot 2C_{29}H_{35}F_3N_2O_3$, and its molecular weight is 1149.29 g/mol.

Its structure is shown below:



It is a white to almost white powder.

MAYZENT is provided as 0.25 mg and 2 mg film-coated tablets for oral use. Each tablet contains 0.25 mg or 2 mg siponimod, equivalent to 0.28 mg or 2.22 mg as 2:1 co-crystal of siponimod and fumaric acid, respectively.

MAYZENT tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, glyceryl behenate, lactose monohydrate, microcrystalline cellulose, with a film coating containing iron oxides (black and red iron oxides for the 0.25 mg strength and red and yellow iron oxides for the 2 mg strength), lecithin (soy), polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Siponimod is an S1P receptor modulator. Siponimod binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

12.2 Pharmacodynamics

Immune System

MAYZENT induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues.

With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90% CI) lymphocyte count of approximately 0.560 (0.271-1.08) cells/nL in a typical CYP2C9*1/*1 or *1/*2, non-Japanese patient, corresponding to 20% to 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing [see *Warnings and Precautions (5.1)*].

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose [see *Warnings and Precautions (5.1)*].

Heart Rate and Rhythm

MAYZENT causes a transient reduction in heart rate and atrioventricular conduction upon treatment initiation [see *Warnings and Precautions (5.3)*]. The maximum decline in heart rate is seen in the first 6 hours post dose. Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise, are not affected by siponimod treatment.

A transient, dose-dependent decrease in heart rate was observed during the initial dosing phase of MAYZENT, which plateaued at doses greater than or equal to 5 mg, and bradyarrhythmic events (AV blocks and sinus pauses) were detected at a higher incidence under MAYZENT treatment, compared to placebo.

No second-degree AV blocks of Mobitz type II or higher degree were observed. Most AV blocks and sinus pauses occurred above the recommended dose of 2 mg, with notably higher incidence under non-titrated conditions compared to dose titration conditions [see *Dosage and Administration (2.2, 2.3)*].

The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

Beta-Blockers

The negative chronotropic effect of coadministration of siponimod and propranolol was evaluated in a dedicated pharmacodynamics (PD)/safety study. The addition of propranolol on top of siponimod at steady-state had less pronounced negative chronotropic effects (less than additive effect) than the addition of siponimod to propranolol at steady state (additive HR effect) [see *Drug Interactions (7.3)*].

Cardiac Electrophysiology

In a thorough QT study with doses of 2 mg (recommended dose) and 10 mg (five times the recommended dose) siponimod at steady-state, siponimod treatment resulted in a prolongation of QT_c, with the maximum mean (upper bound of the two-sided 90% CI) of 7.8 (9.93) ms at 2 mg dose and 7.2 (9.72) ms at 10 mg dose. There was an absence of dose- and exposure-response relationship for QT_c effects with the 5-fold dose and exposures achieved by the supratherapeutic dose. No subject had absolute QT_{cF} greater than 480 ms or ΔQT_{cF} greater than 60 ms for siponimod treatment.

Pulmonary Function

Dose-dependent reductions in absolute forced expiratory volume over 1 second were observed in MAYZENT-treated patients and were greater than in patients taking placebo [see *Warnings and Precautions (5.4)*].

12.3 Pharmacokinetics

Siponimod concentration increases in an apparent dose-proportional manner after multiple once-daily doses of siponimod 0.3 mg to 20 mg. Steady-state plasma concentrations are reached after approximately 6 days of once-daily dosing, and steady-state levels are approximately 2-3-fold greater than the initial dose. An up-titration regimen is used to reach the clinical therapeutic dose of siponimod of 2 mg after 6 days, and 4 additional days of dosing are required to reach the steady-state-plasma concentrations.

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after oral administration of immediate release oral dosage forms of siponimod was about 4 hours (range, 3-8 hours). Siponimod absorption is extensive (greater than or equal to 70%, based on the amount of radioactivity excreted in urine and the amount of metabolites in feces extrapolated to infinity). The absolute oral bioavailability of siponimod is approximately 84%. After administration of siponimod 2 mg once-daily over 10

days, a mean C_{max} of 30.4 ng/mL and mean area under plasma concentration-time curve over dosing interval (AUC_{tau}) of 558 h*ng/mL were observed on Day 10. Steady-state was reached after approximately 6 days of once-daily administration of siponimod.

Food Effect

Food intake resulted in delayed absorption (the median T_{max} increased by approximately 2-3 hours). Food intake had no effect on the systemic exposure of siponimod (C_{max} and AUC). Therefore, MAYZENT may be taken without regard to meals.

Distribution

Siponimod distributes to body tissues with a moderate mean volume of distribution of 124 L. Siponimod fraction found in plasma is 68% in humans. Animal studies show that siponimod readily crosses the blood-brain-barrier. Protein binding of siponimod is greater than 99.9% in healthy subjects and in hepatic and renal impaired patients.

Elimination

Metabolism

Siponimod is extensively metabolized, mainly via CYP2C9 (79.3%), followed by CYP3A4 (18.5%). The pharmacological activity of the main metabolites M3 and M17 is not expected to contribute to the clinical effect and the safety of siponimod in humans.

Excretion

An apparent systemic clearance (CL/F) of 3.11 L/h was estimated in MS patients. The apparent elimination half-life is approximately 30 hours.

Siponimod is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion. Unchanged siponimod was not detected in urine.

Specific Populations

Male and Female Patients

Gender has no influence on siponimod pharmacokinetics (PK).

Racial or Ethnic Groups

The single-dose PK parameters were not different between Japanese and Caucasians healthy subjects, indicating absence of ethnic sensitivity on the PK of siponimod.

Patients with Renal Impairment

No dose adjustments are needed in patients with renal impairment. Mean siponimod half-life and C_{max} (total and unbound) were comparable between subjects with severe renal impairment and healthy subjects. Unbound AUCs were only slightly increased (by 33%), compared to healthy subjects, and it is not expected to be clinically significant. The effects of end-stage renal disease or hemodialysis on the PK of siponimod has not been studied. Due to the high plasma protein binding (greater than 99.9%) of siponimod, hemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations.

Patients with Hepatic Impairment

No dose adjustments for siponimod are needed in patients with hepatic impairment. The unbound siponimod AUC parameters are 15% and 50% higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg single dose studied. The increased unbound siponimod AUC in subjects with moderate and severe hepatic impairment is not expected to be clinically significant. The mean half-life of siponimod was unchanged in hepatic impairment.

Drug Interaction Studies

Siponimod (and Metabolites M3, M17) as a Causative Agent of Interaction

In vitro investigations indicated that siponimod and its major systemic metabolites M3 and M17 do not show any clinically relevant drug-drug interaction potential at the therapeutic dose of 2 mg once-daily for all investigated CYP enzymes and transporters.

Siponimod as an Object of Interaction

CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based PK modeling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated.

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors

The coadministration of fluconazole (moderate CYP2C9 and CYP3A4 dual inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1/*1 healthy volunteers led to a 2-fold increase in the AUC of siponimod. Mean siponimod terminal half-life was increased by 50%. Fluconazole led to a 2- to 4-fold increase in the AUC_{tau,ss} of siponimod across different CYP2C9 genotypes, according to in silico evaluation [see *Drug Interactions (7.5)*].

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inducers

The coadministration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 dual inducer) decreased siponimod AUC_{tau,ss} and C_{max,ss} by 57% and 45%, respectively in CYP2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the AUC_{tau,ss} of siponimod by up to 78% and up to 52%, respectively, across CYP2C9 genotypes, according to in silico evaluation [see *Drug Interactions (7.6)*].

Oral Contraceptives

The effects of coadministration of siponimod 2 mg and 4 mg (twice the recommended dosage) once daily with a monophasic oral contraceptive (OC) containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (18 to 40 years of age; CYP2C9*1/*1 genotype). There were no clinically relevant effects on the PK or PD of the OC. No interaction studies have been performed with OCs containing other progestagens; however, an effect of siponimod on their exposure is not expected.

12.5 Pharmacogenomics

The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUC_{inf} and AUC_{last} was approximately 2- and 4-fold higher in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, respectively, while there was only a minor increase of C_{max} by 21% and 16%, respectively, compared to extensive metabolizers (CYP2C9*1/*1). Mean half-life is prolonged in CYP2C9*2/*3 and CYP2C9*3/*3 carriers (51 hours and 126 hours, respectively).

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1/*1 and CYP2C9*1/*2) MS patients after multiple oral administrations of siponimod. CL/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 genotypes, respectively. The resultant increase in siponimod AUC was approximately 25, 61, 91, and 285% higher in CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 subjects, respectively, as compared to CYP2C9*1/*1 subjects [see *Dosage and Administration (2.1, 2.3) and Contraindications (4)*]. As the apparent clearance estimated for CYP2C9*1/*2 subjects is comparable to that of CYP2C9*1/*1 subjects, similar siponimod exposure is expected for both genotypes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral carcinogenicity studies of siponimod were conducted in mice and rats. In mice administered siponimod (0, 2, 8, or 25 mg/kg/day) for up to 104 weeks, there was an increase in malignant lymphoma in females at all doses and in hemangiosarcoma and combined hemangioma and hemangiosarcoma at all doses in males and females. The lowest dose tested is approximately 5 times the RHD of 2 mg/day, on a body surface area (mg/m²) basis.

In rats, administration of siponimod (0, 10, 30, or 90 mg/kg/day in males; 0, 3, 10, or 30 mg/kg/day in females) for up to 104 weeks, there was an increase in thyroid follicular cell adenoma and combined thyroid follicular cell adenoma and carcinoma in males at the highest dose tested. These findings are considered secondary to liver enzyme induction in rats and are not considered relevant to humans. Plasma siponimod exposure (AUC) at the highest dose tested is approximately 200 times that in humans at the RHD.

Mutagenesis

Siponimod was negative in a battery of *in vitro* (Ames, chromosomal aberration in mammalian cells) and *in vivo* (micronucleus in mouse and rat) assays.

Impairment of Fertility

When siponimod was administered orally (0, 2, 20, or 200 mg/kg) to male rats (mated with untreated females) prior to and throughout the mating period, there was a dose-related increase in precoital interval at all doses. A decrease in implantation sites, an increase in preimplantation loss, and a decrease in the number of viable fetuses were observed at the highest dose tested. The higher no-effect dose for adverse effects on fertility (20 mg/kg) is approximately 100 times the RHD on a mg/m² basis.

When siponimod was administered orally (0, 0.1, 0.3, or 1 mg/kg) to female rats (mated with untreated males) prior to and during mating, and continuing to Day 6 of gestation, no effects on fertility were observed up to the highest dose tested (1 mg/kg). Plasma siponimod exposure (AUC) at the highest dose tested is approximately 16 times that in humans at the RHD.

14 CLINICAL STUDIES

The efficacy of MAYZENT was demonstrated in Study 1, a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry (NCT 01665144).

Patients were randomized to receive either once daily MAYZENT 2 mg or placebo, beginning with a dose titration [*see Dosage and Administration (2.2)*]. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected relapse. MRI evaluations were performed at screening and every 12 months.

The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A prespecified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3-month confirmed worsening of at least 20% from baseline on the timed 25-foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate (relapses/year) and MRI measures of inflammatory disease activity.

Study duration was variable for individual patients (median study duration was 21 months, range 1 day-37 months).

Study 1 randomized 1651 patients to either MAYZENT 2 mg (N = 1105) or placebo (N = 546); 82% of MAYZENT-treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was 6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy.

Results are presented in Table 4. MAYZENT was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.79, $p < 0.0134$; see Figure 1). MAYZENT did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo. Patients treated with MAYZENT had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal p -value < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although MAYZENT had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of MAYZENT in patients with non-active SPMS was not statistically significant (see Figure 2).

Table 4 Clinical and MRI Results From Study 1

	MAYZENT	PLACEBO
Clinical Outcomes		
Proportion of patients with confirmed disability progression ¹	26%	32%
Relative risk reduction	21% ($p = 0.0134$)*	
Absolute risk Reduction	6%	
Proportion of patients with confirmed worsening in timed 25-foot walk	40%	41%
	$p = NS$	
Annualized relapse rate ²	0.071	0.160
Relative reduction (%)	55% ($p < 0.01$)^	
Absolute reduction	0.089	
	$p < 0.01$ ^	
MRI Endpoints		
Change from baseline in T2 lesion volume (mm ³) (95% CI) ³	184 (54; 314)	879 (712; 1047)
	$p < 0.01$ ^	

All analyses are based on the full analysis set (FAS), which includes all randomized subjects who took at least one dose of study medication. p-values are two-sided.

(¹) Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5. Progression confirmed at 3 months. Cox proportional hazard model.

(²) Defined as the average number of confirmed relapses per year (estimated from negative binomial regression model for recurrent events).

(³) Adjusted mean averaged over Months 12 and 24.

*Statistically significant.

NS, Not statistically significant.

^ Nominal p value, not corrected for multiple comparisons.

Figure 1 Time to Confirmed Disability Progression Based on EDSS (Study 1)

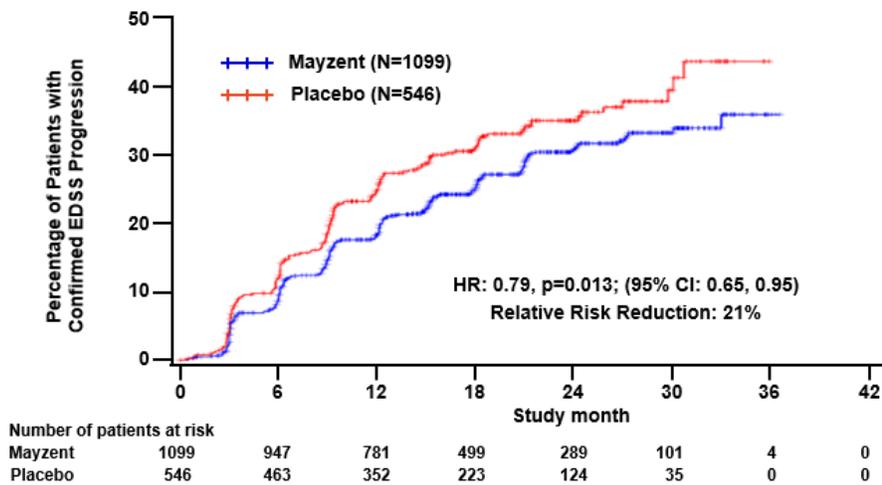
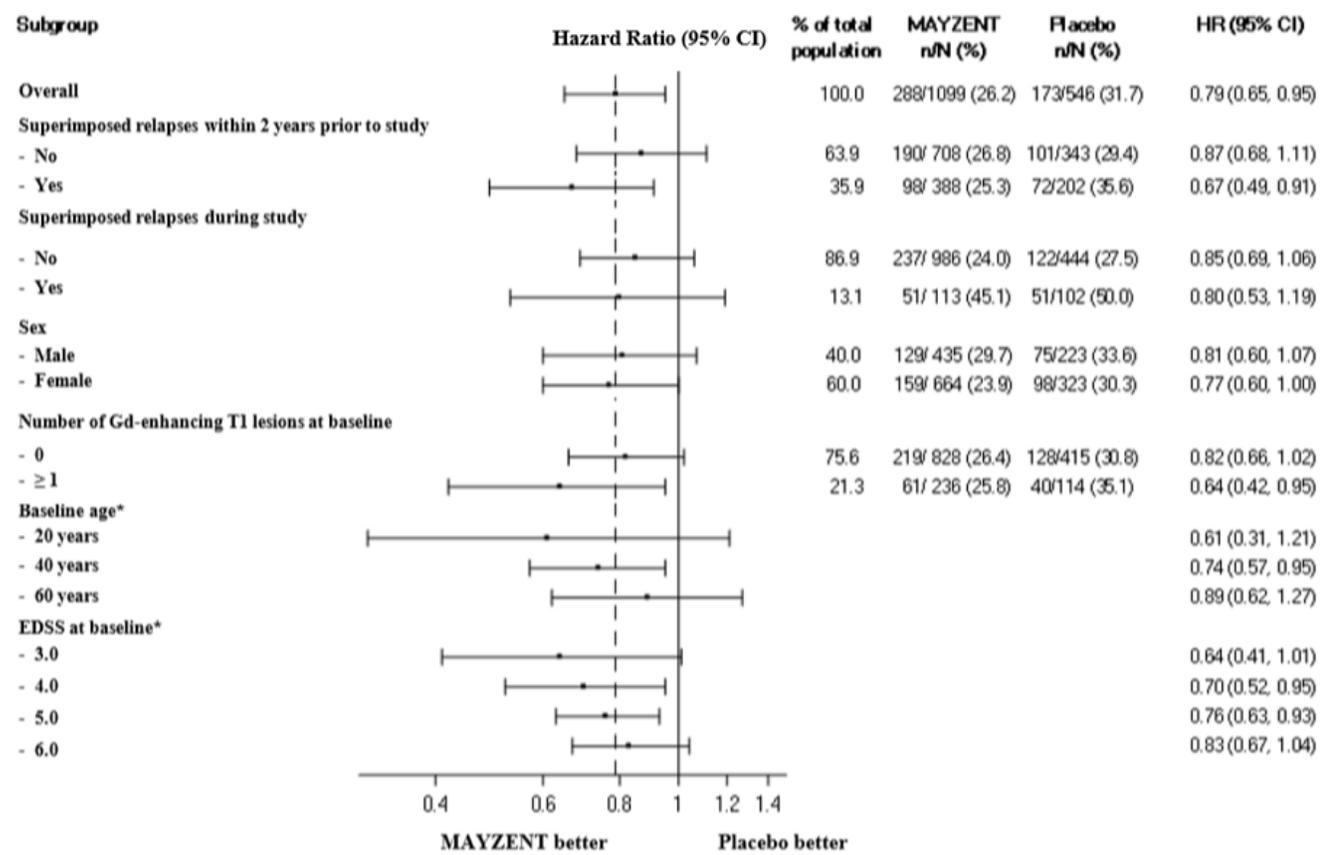


Figure 2 Time to Confirmed Disability Progression Based on EDSS (Study 1), Subgroup Analysis



*HR and 95% CI presented are model-based estimates for a range of values of age and EDSS.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MAYZENT film-coated tablets are supplied as follows:

0.25 mg tablet: Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'T' on other side.

Starter Pack* – blister card of twelve 0.25 mg tablets in a calendarized blister wallet.....NDC 0078-0979-12

*This starter pack is only intended for patients who will receive the 2 mg maintenance dosage.

Bottle of 28 tablets.....NDC 0078-0979-50

2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with  on one side and 'II' on other side.

Bottle of 30 tablets.....NDC 0078-0986-15

16.2 Storage and Handling

Unopened Containers

Store MAYZENT 0.25 mg and 2 mg film-coated tablets in a refrigerator between 2°C to 8°C (36°F to 46°F). After pharmacy dispensing to patient, MAYZENT 0.25 mg and 2 mg film-coated tablets may be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 3 months.

Opened Containers

Bottles

MAYZENT 0.25 mg and 2 mg film-coated tablets may be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 3 months. Do not refrigerate after opening.

Starter Pack/Blister Card

MAYZENT 0.25 mg film-coated tablets may be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 3 months. Do not refrigerate after opening. Store in original calendarized blister wallet container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

Tell patients not to discontinue MAYZENT without first discussing this with the prescribing physician. Advise patients to contact their physician if they accidentally take more MAYZENT than prescribed.

Instruct patients to administer tablets whole; do not split, crush, or chew MAYZENT tablets.

Risk of Infections

Inform patients that they may have an increased risk of infections, some of which could be life-threatening, when taking MAYZENT, and that they should contact their physician if they develop symptoms of infection [see *Warnings and Precautions (5.1)*]. Advise patients that the use of some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with MAYZENT and MAYZENT should be paused 1 week prior and until 4 weeks after a planned vaccination. Recommend that patients postpone treatment with MAYZENT for at least 1 month after VZV vaccination. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection.

Macular Edema

Advise patients that MAYZENT may cause macular edema, and that they should contact their physician if they experience any changes in their vision while taking MAYZENT [see *Warnings and Precautions (5.2)*]. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema is increased.

Cardiac Effects

Advise patients that initiation of MAYZENT treatment results in transient decrease in heart rate [see *Warnings and Precautions (5.3)*]. Inform patients that to reduce this effect, dosage titration is required. Advise patients that dosage titration is also required if a dose is missed for more than 24 hours during the titration or if 4 or more consecutive daily maintenance doses are missed [see *Dosage and Administration (2.2, 2.3, 2.5)* and *Warnings and Precautions (5.3)*]. Inform certain patients with certain pre-existing cardiac conditions that they will need to be observed in the doctor's office or other facility for at least 6 hours after the first dose and after reinitiation if treatment is interrupted or discontinued for certain periods [see *Dosage and Administration (2.4)*].

Respiratory Effects

Advise patients that they should contact their physician if they experience new onset or worsening of dyspnea [see *Warnings and Precautions (5.4)*].

Liver Injury

Inform patients that MAYZENT may increase liver enzymes. Advise patient that they should contact their physician if they experience any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment [see *Warnings and Precautions (5.5)*].

Cutaneous Malignancies

Inform patients that the risk of basal cell carcinoma is increased with the use of MAYZENT and that cases of melanoma and squamous cell carcinoma have been reported. Advise patients that any suspicious skin lesions should be promptly evaluated. Advise patients to limit exposure to sunlight and ultraviolet light by wearing protective clothing and using a sunscreen with a high protection factor [see *Warnings and Precautions (5.6)*].

Pregnancy and Fetal Risk

Inform patients that, based on animal studies MAYZENT may cause fetal harm [see *Warnings and Precautions (5.8)*]. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with MAYZENT and for 10 days after stopping MAYZENT. Advise a female patient to immediately inform that prescriber if she is pregnant or planning to become pregnant [see *Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1, 8.3)*].

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological sequelae [*see Warnings and Precautions (5.9)*].

Severe Increase in Disability After Stopping MAYZENT

Inform patients that severe increase in disability has been reported after discontinuation of another S1P receptor modulator like MAYZENT. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of MAYZENT [*see Warnings and Precautions (5.11)*].

Immune System Effects After Stopping MAYZENT

Advise patients that MAYZENT continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 to 4 weeks after the last dose [*see Warnings and Precautions (5.12)*].

Storage and Handling

Inform patients that MAYZENT may be stored at room temperature for up to 3 months. If patients need to store MAYZENT for more than 3 months, containers should remain unopened and stored in a refrigerator until use [*see How Supplied/Storage and Handling (16.2)*].

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East Hanover, New Jersey 07936

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MEDICATION GUIDE
MAYZENT (Mā'zěnt)
(siponimod)
tablets, for oral use

What is the most important information I should know about MAYZENT?

- 1. MAYZENT may cause serious side effects, including: Slow heart rate (bradycardia or bradyarrhythmia) when you start taking MAYZENT.** MAYZENT can cause your heart rate to slow down, especially after you take your first dose. You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of MAYZENT.

During the initial updosing period (4 days for the 1 mg daily dose or 5 days for the 2 mg daily dose), if you miss 1 or more doses of MAYZENT, you need to restart the updosing. Call your healthcare provider if you miss a dose of MAYZENT. See **"How should I take MAYZENT?"**

- 2. Infections.** MAYZENT can increase your risk of serious infections that can be life-threatening and cause death. MAYZENT lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 to 4 weeks of stopping treatment. Your healthcare provider should review a recent blood test of your white blood cells before you start taking MAYZENT.

Call your healthcare provider right away if you have any of these symptoms of an infection during treatment with MAYZENT and for 3 to 4 weeks after your last dose of MAYZENT:

- fever
- tiredness
- body aches
- chills
- nausea
- vomiting
- headache with fever, neck stiffness, sensitivity to light, nausea, confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)

- 3.** A problem with your vision called macular edema. Macular edema can cause some of the same vision symptoms as a multiple sclerosis (MS) attack (optic neuritis). You may not notice any symptoms with macular edema. If macular edema happens, it usually starts in the first 1 to 4 months after you start taking MAYZENT. Your healthcare provider should test your vision before you start taking MAYZENT and any time you notice vision changes during treatment with MAYZENT. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

Call your healthcare provider right away if you have any of the following:

- blurriness or shadows in the center of your vision
- a blind spot in the center of your vision
- sensitivity to light
- unusually colored (tinted) vision

See "What are the possible side effects of MAYZENT?" for more information about side effects.

What is MAYZENT?

MAYZENT is a prescription medicine that is used to treat relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

It is not known if MAYZENT is safe and effective in children.

Who should not take MAYZENT?

Do not take MAYZENT if you:

- have a CYP2C9*3/*3 genotype. Before starting treatment with MAYZENT, your CYP2C9 genotype should be determined by your healthcare provider. Ask your healthcare provider if you are not sure.
- have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months
- have certain types of heart block or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker

What should I tell my healthcare provider before taking MAYZENT?

Before taking MAYZENT, tell your healthcare provider about all of your medical conditions, including if you:

- have an irregular or abnormal heartbeat
- a history of stroke or other diseases related to blood vessels in the brain
- breathing problems, including during your sleep
- a fever or infection, or you are unable to fight infections due to a disease or taking medicines that lower your immune system. Tell your healthcare provider if you have had chickenpox or have received the vaccine for chickenpox. Your healthcare provider may do a blood test for chickenpox virus. You may need to get the full course of vaccine for chickenpox and then wait 1 month before you start taking MAYZENT.
- have slow heart rate
- have liver problems

- have diabetes
- have eye problems, especially an inflammation of the eye called uveitis
- had or now have a type of skin cancer called basal cell carcinoma (BCC), melanoma, or squamous cell carcinoma
- have high blood pressure
- are pregnant or plan to become pregnant. MAYZENT may harm your unborn baby. Talk to your healthcare provider right away if you become pregnant while taking MAYZENT or if you become pregnant within 10 days after you stop taking MAYZENT.
 - If you are a woman who can become pregnant, you should use effective birth control during your treatment with MAYZENT and for at least 10 days after you stop taking MAYZENT.
- are breastfeeding or plan to breastfeed. It is not known if MAYZENT passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take MAYZENT.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you:

- take medicines to control your heart rhythm (antiarrhythmics), or blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers)
- take medicines that affect your immune system, such as beta-interferon or glatiramer acetate, or any of these medicines that you took in the past
- have recently received a live vaccine. You should avoid receiving **live** vaccines during treatment with MAYZENT. MAYZENT should be stopped 1 week before and for 4 weeks after receiving a live vaccine. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Vaccines may not work as well when given during treatment with MAYZENT.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

Using MAYZENT and other medicines together may affect each other causing serious side effects.

How should I take MAYZENT?

The daily maintenance dose of MAYZENT is either 1 mg or 2 mg, depending on your CYP2C9 genotype. Ask your healthcare provider if you are not sure about your daily maintenance dose.

Do not split, crush, or chew MAYZENT tablets; take tablets whole.

Start your treatment with MAYZENT using the following titration schedule:

For the 1 mg daily maintenance dose:	Tablets a day
Day 1	1 x 0.25 mg tablet
Day 2	1 x 0.25 mg tablet
Day 3	2 x 0.25 mg tablet
Day 4	3 x 0.25 mg tablet
Day 5 and every day after	4 x 0.25 mg tablet
For the 2 mg daily maintenance dose, use the starter pack:	Tablets a day
Day 1	1 x 0.25 mg tablet
Day 2	1 x 0.25 mg tablet
Day 3	2 x 0.25 mg tablet
Day 4	3 x 0.25 mg tablet
Day 5	5 x 0.25 mg tablet
Day 6 and every day after	1 x 2 mg tablet

- Take MAYZENT exactly as your healthcare provider tells you. Do not change your dose or stop taking MAYZENT unless your healthcare provider tells you to.
- Take MAYZENT 1 time each day.
- Take MAYZENT with or without food.
- If you miss 1 or more doses of MAYZENT **during** the initial dose titration, you need to restart the medication.
- If you miss a dose of MAYZENT **after** the initial dose-titration, take it as soon as you remember.
- If MAYZENT treatment is stopped for 4 days in a row, treatment has to be restarted with the titration.
- **Do not stop taking MAYZENT without talking with your healthcare provider first.**

What are the possible side effects of MAYZENT?

MAYZENT may cause serious side effects, including:

- **See "What is the most important information I should know about MAYZENT?"**
- **increased blood pressure.** Your healthcare provider should check your blood pressure during treatment with MAYZENT.
- **liver problems.** MAYZENT may cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking MAYZENT. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
 - nausea
 - vomiting
 - stomach pain
 - tiredness
 - loss of appetite
 - your skin or the whites of your eyes turn yellow
 - dark urine
- **breathing problems.** Some people who take MAYZENT have shortness of breath. Call your healthcare provider right away if you have new or worsening breathing problems.
- **swelling and narrowing of the blood vessels in your brain.** A condition called PRES (Posterior Reversible Encephalopathy Syndrome) has happened with drugs in the same class. Symptoms of PRES usually get better when you stop taking MAYZENT. However, if left untreated, it may lead to a stroke. Call your healthcare provider right away if you have any of the following symptoms:
 - sudden severe headache
 - sudden confusion
 - sudden loss of vision or other changes in your vision
 - seizure
- **severe worsening of multiple sclerosis after stopping MAYZENT.** When MAYZENT is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your doctor before you stop taking MAYZENT for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping MAYZENT.
- **types of skin cancer called basal cell carcinoma (BCC), melanoma, and squamous cell carcinoma.** Tell your doctor if you have any changes in the appearance of your skin, including changes in a mole, a new darkened area on your skin, a sore that does not heal, or growths on your skin, such as a bump that may be shiny, pearly white, skin-colored, or pink. Your doctor should check your skin for any changes during treatment with MAYZENT. Limit the amount of time you spend in sunlight and ultraviolet (UV) light. Wear protective clothing and use a sunscreen with a high sun protection factor.

The most common side effects of MAYZENT include:

- headache
- high blood pressure (hypertension)
- abnormal liver tests

Tell your healthcare provider if you have any side effects that bother you or that do not go away.

These are not all of the possible side effects of MAYZENT. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAYZENT?

Unopened Containers

MAYZENT 0.25 mg and 2 mg tablets may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months. If you need to store MAYZENT tablets for more than 3 months, containers should remain unopened and stored in a refrigerator between 36°F to 46°F (2°C to 8°C) until use.

Opened Containers

Bottles

MAYZENT 0.25 mg and 2 mg tablets may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months. Do not refrigerate after opening.

Starter Pack/Blister Card

MAYZENT 0.25 mg tablets may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months. Do not refrigerate after opening. Store in original calendarized blister wallet container.

Keep MAYZENT and all medicines out of the reach of children.

General information about the safe and effective use of MAYZENT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MAYZENT for a condition for which it was not prescribed. Do not give MAYZENT to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about MAYZENT that is written for health professionals.

What are the ingredients in MAYZENT?

Active ingredient: siponimod

Inactive ingredients: colloidal silicon dioxide, crospovidone, glyceryl behenate, lactose monohydrate, microcrystalline cellulose, with a film coating containing iron oxides (black and red iron oxides for the 0.25 mg strength and red and yellow iron oxides for the 2 mg strength), lecithin (soy), polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

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For more information, go to www.novartis.us or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration

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