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

----------INDICATIONS AND USAGE----------

MAYZENT is a sphingosine 1-phosphate 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)
- 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)
- Increased Blood Pressure (BP): Monitor BP during treatment. (5.6)
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 10 days after stopping MAYZENT. (5.7)

----------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----------

- Vaccines: 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: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 antineoplastic, 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)]*.

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.

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 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 postdose 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 & 'T' on other side.

2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with ⏻ on one side & '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%-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 complete blood count (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 3-4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period *[see Warnings and Precautions (5.11)]*.

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 1, 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 a 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 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 Antineoplastic, 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%

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