PDL DRUG REVIEW

Proprietary Name: Mayzent®
Common Name: siponimod
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Aubagio	Preferred with Conditions
Gilenya	Preferred with Conditions
Tecfidera	Preferred with Conditions

Summary

Pharmacology/Usage: Siponimod, the active ingredient of Mayzent®, is a sphingosine-1-phosphate (S1P) receptor modulator. It binds with high affinity to S1P receptors 1 and 5 and blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. While the mechanism by which siponimod exerts its effect in multiple sclerosis is not known, it may involve reduction of lymphocyte migration into the CNS.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risk associated with use in pregnant women. Based on animal data and its mechanism of action, Mayzent® can cause fetal harm when given to a pregnant woman. Women of childbearing potential should use effective contraception during treatment and for at least 10 days after the discontinuation of treatment. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 0.25mg, 2mg. Store unopened containers in the refrigerator.

Recommended Dosage: Before starting treatment, the following should be assessed.

- Test patients for CYP2C9 variants to determine CYP2C9 genotype. An FDA-cleared or FDA-approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.
- Review results of a recent complete blood count (CBC).
- Obtain an evaluation of the fundus, including the macula, in an ophthalmic evaluation,
- Obtain recent (i.e. within last 6 months) transaminase and bilirubin levels.
- Obtain an electrocardiogram (ECG) to determine if pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist and first-dose monitoring is recommended. Determine whether patients are taking drugs that could slow heart rate or atrioventricular condition.
- Review 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 starting treatment with Mayzent®

- Test patients for antibodies to varicella zoster virus (VZV) before starting Mayzent®; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Mayzent®.

In patients with CYP2C9 genotypes *1/*1, *1/*2, or *2/*2, start Mayzent® with a 5-day titration of 0.25mg on day 1 and 2, 0.5mg on day 3, 0.75mg on day 4, and 1.25mg on day 5. After treatment titration, the recommended maintenance dose is 2mg PO QD starting on day 6.

Adjust dosage in patients with CYP2C9 genotypes *1/*3 or *2/*3 genotype. In this population, start with a 4-day titration including 0.25mg on day 1 and 2, 0.50mg on day 3, and 0.75mg on day 4. After treatment titration, the recommended maintenance dosage is 1mg PO QD starting on day 5.

After the initial titration is complete, if Mayzent® treatment is interrupted for ≥4 consecutive daily doses, re-start treatment with day 1 of the titration regimen. Also, complete first-dose monitoring in patients for whom it is recommended.

As initiation of Mayzent® 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 MI or heart failure. 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 measurements. Obtain an ECG in these patients at the end of the day 1 observation period.

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 45bpm
- 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, of if ECG 6 hours post-dose shows new onset second degree or higher AV block or QTc ≥500msec, start 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 during treatment initiation, if treatment with Mayzent® is considered in patients with some pre-existing heart and cerebrovascular conditions; 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; receiving concurrent therapy with drugs that slow heart rate or AV conduction.

Dose adjustments are not required with renal or hepatic impairment.

Drug Interactions: Mayzent® has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Use caution during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks after administration. Treatment with Mayzent® after alemtuzumab is not recommended. Mayzent® can generally be started immediately after discontinuation of beta interferon or glatiramer.

Mayzent® has not been studied in patients taking QT prolonging drugs. Class Ia (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmic 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. Due to the potential additive effects on heart rate, treatment with Mayzent® should generally not be started in

patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers, or other drugs that may decrease heart rate (e.g. ivabradine, digoxin). 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.

Use caution when Mayzent® is started in patients receiving beta-blocker therapy due to the additive effects on lowering heart rate. Temporary interruption of the beta-blocker treatment may be needed prior to starting Mayzent®. Beta-blocker treatment can be started in patients receiving stable doses of Mayzent®.

During and for up to 1 month after discontinuation of Mayzent® treatment, vaccinations may be less effective. Thus, Mayzent® treatment should be paused 1 week prior and for 4 weeks after vaccination. The use of live attenuated vaccines may carry the risk of infection and should thus be avoided during Mayzent® treatment and for up to 4 weeks after discontinuation of treatment with Mayzent®.

Due to significant increases 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. Due to 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 a 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 inhibitors or 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.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Mayzent® 2mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included headache (1%), hypertension (4%), transaminase increased (8%), falls (1%), edema peripheral (4%), nausea (3%), dizziness (2%), diarrhea (2%), bradycardia (3%), and pain in extremity (2%). Macular edema (1.6%) was also reported.

Mayzent® causes a dose-dependent reduction in peripheral lymphocyte count to 20-30% of baseline values. Thus, treatment may increase the risk of infections, some serious in nature. Life-threatening and rare fatal infections have occurred in association with Mayzent®. Before starting treatment with Mayzent®, results from a recent blood count should be reviewed. Initiation of treatment should be delayed in patients with severe active infection until resolution. There have been no cases of progressive multifocal leukoencephalopathy (PML) in Mayzent®-treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other MS therapies and has been associated with some risk factors. If PML is suspected, Mayzent® should be suspended until PML has been excluded.

Macular edema was reported with Mayzent®. Patients with a history of uveitis and patients with DM 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 addition to the exam of the fundus, including the macular, prior to treatment, MS patients with DM or a history of uveitis should have regular follow-up exams.

Bradyarrhythmia and atrioventricular conduction delays occur transiently with initiation of Mayzent® therapy. The following are treatment-initiation recommendations: obtain an ECG in all patients; a dose titration is recommended for initiation of treatment in all patients; in patients with sinus bradycardia, 1st or 2nd degree AV block, or history of MI or heart failure with onset >6 months prior to initiation, ECG testing and 1st-dose monitoring is recommended; as bradycardia may be poorly tolerated in patients with a history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, Mayzent® is not recommended in these patients; use of Mayzent® in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment; experience with Mayzent® is limited in patients receiving concurrent therapy with

drugs that decrease heart-rate and concomitant use of these drugs during Mayzent® initiation may be associated with severe bradycardia and heart block.

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were seen in Mayzent®-treated patients as early as 3 months after the start of treatment. There is not sufficient information to determine the reversibility of the decreases in FEV1 after drug discontinuation. Spirometric evaluation of respiratory function should be performed during therapy with Mayzent® if clinically indicated.

Elevations of transaminases may occur in Mayzent®-treated patients. Patients who develop symptoms suggestive of hepatic dysfunction should have their liver enzymes checked and treatment should be discontinued if significant liver injury is confirmed. While there are no data to establish that patients with pre-existing 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.

Hypertension was reported as an adverse reaction (Mayzent® minus placebo= 3.3%). Blood pressure should be monitored during treatment with Mayzent® and managed appropriately.

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. Such events have not been reported for Mayzent®-treated patients in the development program. 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, Mazyent® should be discontinued.

Severe exacerbations of disease, including disease rebound, has been rarely reported after discontinuation of a 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 when they discontinue Mayzent® and appropriate treatment should be started.

Contraindications: A CYP2C9 *3/*3 genotype (approximately 0.4%-0.5% of Caucasians and less in others); In the last 6 months experienced MI, 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

Manufacturer: Novartis Pharmaceuticals

Analysis: The efficacy of Mayzent® was demonstrated in a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive MS (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to the study, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry (N=1651). The median age of randomized patients was 49 years, with 95% being white and 60% being female. The median disease duration was 16 years, and the median EDSS score at baseline was 6. In addition, 36% of patients had ≥1 relapse in the 2 years prior to study entry, 22% of those patients with available imaging had ≥1 gadolinium-enhancing lesions on their baseline MRI scan, and 78% of patients had been previously treated with an MS therapy.

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 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. Results suggested that Mayzent® was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (HR 0.79; $p<0.0134$). Mayzent® did not significantly delay the time to 20% deterioration in the timed 25-foot walk compared to placebo. In addition, patients treated with Mayzent® had a 55% relative reduction in the annualized relapse rate (ARR) compared to placebo (nominal $p<0.0001$). The absolute reduction in the ARR was 0.089. While Mayzent® had a significant effect on disability progression compared to placebo in patients with active

SPMS, the effect of Mayzent® in patients with non-active SPMS was not statistically significant. Results can be seen in the table below, which was adapted from the prescribing information.

	Mayzent®	Placebo
Clinical Outcomes		
Proportion of patients with confirmed disability progression	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	0.071	0.160
Relative reduction	55%; (nominal p<0.01)	
Absolute reduction	0.089	
	nominal p<0.01	
MRI Endpoints		
Change from baseline in T2 lesion volume (mm^3)	184	879
	nominal p<0.01	

Place in Therapy: Mayzent® is an oral tablet indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It is recommended to test patients for CYP2C9 variants to determine CYP2C9 genotype before starting treatment. An FDA-cleared or FDA-approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available. Dosing is based on CYP2C9 genotypes. In a clinical trial, it significantly decreased the proportion of patients with confirmed disability progression at 3 months as compared with placebo; however, it did not demonstrate a significant effect on the timed 25-foot walk test. Comparator studies with other active agents indicated for MS were not found.

There is no evidence at this time that Mayzent® is safer or more effective than the currently preferred, more cost-effective medications. It is therefore recommended that Mayzent® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

Reference

[1] Mayzent [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp; 2019.