PDL DRUG REVIEW

Proprietary Name: Ponvory®
Common Name: ponesimod
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Gilenya	Preferred with Conditions
Mayzent	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Ponesimod, the active ingredient of Ponvory®, is a sphingosine 1-phosphate (S1P) receptor 1 modulator that binds with high affinity to S1P receptor 1. Ponesimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis is not known but 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 and well-controlled studies of use in pregnant women. Before initiation of Ponvory® treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment and for one week after stopping treatment. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 2mg, 3mg, 4g, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, and 20mg. Swallow whole.

Recommended Dosage: Before initiation of Ponvory® treatment, assess the following:

- Complete Blood Count (CBC)- Obtain a recent (i.e. within the last 6 months) CBC, including lymphocyte count.
- Cardiac Evaluation-
    - Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought and first-dose monitoring is recommended.
    - Determine whether patients are taking drugs that could slow heart rate of atrioventricular (AV) conduction.
- Liver Function Tests- Obtain recent (i.e. within the last 6 months) transaminase and bilirubin levels.
- Ophthalmic Evaluation- Obtain an evaluation of the fundus, including the macula.
- Current or prior medications with immune system effects- 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 Ponvory®.

- Vaccinations- Test for antibodies to varicella zoster virus (VZV) before starting Ponvory®; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Ponvory®. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of Ponvory®.

A starter pack must be used for patients initiating treatment with Ponvory®. Initiate Ponvory® treatment with a 14-day titration. Start with one 2mg tablet PO QD and progress with the titration schedule that can be found in the prescribing information. After dose titration is complete, the recommended maintenance dosage is 20mg PO QD starting on day 15. Interruption during treatment, especially during titration, is not recommended; however, refer to the prescribing information for further information if missed doses occur.

Because initiation of Ponvory® treatment results in a decrease in heart rate (HR), first-dose 4-hour monitoring is recommended for patients with sinus bradycardia (HR <55 beats per minute [bpm]), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure occurring more than 6 months prior to treatment initiation and in stable condition.

Administer the first dose of Ponvory® in a setting where resources to appropriately manage symptomatic bradycardia are available. Monitor patients for 4 hours after the first dose for signs and symptoms of bradycardia with a minimum of hourly pulse and blood pressure measurements. Obtain an ECG in these patients prior to dosing and at the end of the 4-hour observation period. If any of the following are present after 4 hours (even in the absence of symptoms), continue monitoring until the abnormality resolves:

- The heart rate 4 hours post-dose is less than 45bpm
- The heart rate 4 hours post-dose is at the lowest value post-dose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 4 hours post-dose shows new onset second-degree or higher AV block

If post-dose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or if ECG 4 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 symptoms have resolved if no pharmacologic treatment is required. If pharmacologic treatment is required, continue monitoring overnight and repeat 4-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 Ponvory® is considered in patients:

- With some pre-existing heart and cerebrovascular conditions
- With a prolonged QTc interval before dosing or during the 4-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsade de pointes
- Receiving concurrent therapy with drugs that slow heart rate or AV conduction

Dosage adjustment is not required with mild hepatic impairment. Use is not recommended in patients with moderate or severe hepatic impairment, as the risk of adverse reactions may be greater.

Drug Interactions: Ponvory® has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be exercised during concomitant administration due to the risk of additive immune effects. Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with Ponvory® after alemtuzumab is not recommended. Ponvory® can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Ponvory® 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 Ponvory® is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with Ponvory® should generally not be started in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering CCBs (e.g. verapamil, diltiazem) or other drugs that may decrease heart rate (e.g. digoxin). If treatment with Ponvory® is considered, seek advice from a cardiologist.

Use caution when Ponvory® is started 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 before starting Ponvory®. Beta-blocker treatment can be started in patients receiving stable doses of Ponvory®.

During and for up to 1-2 weeks after discontinuation of Ponvory®, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should thus be avoided during Ponvory® treatment and for 1-2 weeks after discontinuation of treatment with Ponvory®.

Concomitant use of strong CYP3A4 and UGT1A1 inducers (e.g. rifampin, phenytoin, carbamazepine) may decrease the systemic exposure of ponesimod. It is not clear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance. Concomitant use of Ponvory® with strong CYP3A4 and UGT1A1 inducers is not recommended.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ponvory®) minus reported % incidence for teriflunomide. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included upper respiratory infection (3%), hepatic transaminase elevation (11%), hypertension (1%), urinary tract infection (1%), dyspnea (4%), dizziness (2%), cough (2%), pain in extremity (1%), somnolence (1%), pyrexia (1%), C-reactive protein increased (1%), hypercholesterolemia (1%), and vertigo (1%).

Ponvory® causes a dose-dependent reduction in peripheral lymphocyte count to 30-40% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissue. Ponvory® may thus increase the susceptibility to infections. Life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators. Before starting treatment with Ponvory®, results from a recent complete blood count including lymphocyte count should be reviewed. In addition, progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with a S1P receptor modulator and other MS therapies and has been associated with some risk factors Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with Ponvory® should be suspended until PML has been excluded.

Since initiation of Ponvory® treatment results in a transient decrease in heart rate and AV conduction delays, an up-titration scheme must be used to reach the maintenance dose of Ponvory®. The phase 3 trial did not include patients who had a resting HR <50 bpm or baseline ECG; MI or unstable ischemic heart disease in the last 6 months; cardiac failure or presence of any severe cardiac disease; cardiac conduction or rhythm disorders either in history or observed at screening; Mobitz type II second degree AV block or higher-grade AV block observed at screening; QTcF interval >470ms (females) and >450ms (males) observed at screening; history of syncope associated with cardiac disorders; or uncontrolled systemic arterial hypertension.

Dose-dependent reductions in FEV1 and reductions in diffusion lung capacity for carbon monoxide were observed in patients treated with Ponvory®, mostly occurring in the first month after treatment initiation. There is not sufficient information to determine the reversibility of the decrease in FEV1 or forced vital capacity after treatment discontinuation. Ponvory® should be used with caution with severe respiratory disease (i.e. pulmonary fibrosis, asthma, and COPD). Spirometric evaluation of respiratory function should be performed during Ponvory® treatment as clinically indicated.

Elevations of transaminases may occur in patients treated with Ponvory®. Obtain transaminase and bilirubin levels before the start of treatment. Check hepatic enzymes if patients develop symptoms suggestive of hepatic dysfunction.

In one phase 3 study, Ponvory®-treated patients had an average increase of 2.9mmHg in systolic BP and 2.8mmHg in diastolic BP compared to 2.8mmHg and 3.1mmHg in patients receiving teriflunomide, respectively. An increase in BP was first detected about 1 month after the beginning of treatment. Blood pressure should be monitored during treatment and managed appropriately.

Cases of basal cell carcinoma and other skin malignancies have been reported in patients treated with S1P receptor modulators, including Ponvory®. In one phase 3 study, the incidence of basal cell carcinoma was 0.4% with Ponvory® vs 0.2% with teriflunomide. Periodic skin examination is recommended for all patients, especially those with risk factors for skin cancer. Exposure to sunlight and UV 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 Ponvory®.

S1P receptor modulators, including Ponvory®, have been associated with an increased risk of macular edema. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if a patient reports any change in vision while on Ponvory® treatment. Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during therapy with S1P receptor modulators, including Ponvory®. Thus, these patients should have regular follow-up exams of the fundus, including of the macula, during Ponvory® treatment.

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 Ponvory®-treated patients in the development program. If PRES is suspected, Ponvory® should be discontinued.

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The potential of severe exacerbation of disease should be considered after stopping Ponvory®. Observe patients for a severe increase in disability upon Ponvory® discontinuation and start appropriate treatment if needed.

Contraindications: In patients who:

- In the last 6 months have experienced myocardial infarction (MI), unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Have presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, or sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker

Manufacturer: Janssen Pharmaceuticals, Inc

Analysis: The safety and efficacy of Ponvory® were assessed in a randomized, double-blind, parallel group, active-controlled superiority study that included patients with relapsing forms of MS who were treated for 108 weeks. Patients included had an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at baseline, had experienced at least 1 relapse within the year prior, or two relapses within the prior 2 years, or who had at least one gadolinium-enhancing (Gd-enhancing) lesion on a brain MRI within the prior 6 months or at baseline. Neurological exams were performed at baseline, every 3 months during the study, and at the time of a suspected relapse. Brain MRI scans were performed at baseline and at weeks 60 and 108.

Patients (N=1133) were randomized to receive either Ponvory® or teriflunomide 14mg. At baseline, the mean age of patients was 37 years, while 97% were white and 65% were female. The mean disease duration was 7.6 years, the mean number of relapses in the previous year was 1.3 and the mean EDSS score was 2.6. In addition, 57% had not received any prior non-steroid treatments for MS and 42.6% had one or more Gd-enhancing T1 lesions (mean 2.0) on the baseline MRI scan.

The primary endpoint was the annualized relapse rate (ARR) over the study period, with additional outcomes assessed including the number of new Gd-enhancing T1 lesions from baseline to week 108, the number of new or enlarging T2 lesions from baseline to week 108, and the time to 3-month and 6-month confirmed disability

progression. A confirmed disability progression was defined as an increase of at least 1.5 in EDSS for patients with a baseline EDSS score of 0, an increase of at least 1.0 in EDSS for patients with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for patients with a baseline EDSS score of at least 5.5, which was confirmed after 3 and 6 months.

Results suggested that the ARR was statistically significantly lower in the Ponvory® group than in the teriflunomide group. The number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in the patients treated with Ponvory® than in patients who received teriflunomide. There was no statistically significant difference in the 3-month and 6-month confirmed disability progression outcomes between Ponvory® and teriflunomide over 108 weeks. Results can be seen in the table below, which was adapted from the prescribing information.

	Ponvory® (N=567)	Teriflunomide 14mg (N=566)
Clinical Endpoints		
ARR	0.202	0.290
Relative reduction	30.5% (p=0.0003)	
% of patients without relapse	70.7%	60.6%
Proportion with 3-month confirmed disability progression	10.8%	13.2%
Hazard Ratio	0.83 (p=0.29)	
MRI Endpoints		
Mean # of new or enlarging T2 hyperintense lesions per year	1.40	3.16
Relative reduction	55.7% (p<0.0001)	
Mean # of T1 Gd-enhancing lesions per MRI	0.18	0.43
Relative reduction	58.5% (p<0.0001)	

Place in Therapy: Ponvory®, an oral S1P receptor 1 modulator, is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Due to a decrease in heart rate with Ponvory® initiation, a first-dose 4-hour monitoring is recommended for patients with sinus bradycardia, first-or second-degree AV block, or a history of MI or heart failure occurring more than 6 months prior to treatment initiation and in stable condition. Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy during treatment initiation if treatment is started in certain patients (e.g. with prolonged QTc interval or with some pre-existing heart and cerebrovascular conditions). A phase 3 double-blind, superiority study compared Ponvory® with teriflunomide 14mg and results suggested that the ARR was statistically significantly lower in those treated with Ponvory® as compared with teriflunomide 14mg. While no statistically significant differences were observed in confirmed disability progression, the number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in the Ponvory® group than in the teriflunomide group.

There is some evidence to suggest that Ponvory® may be more effective than teriflunomide 14mg for reducing the primary endpoint of annualized relapsed rate in a phase 3 study, as well as for some secondary MRI endpoints; however, there is no evidence at this time to support that Ponvory® is safer than teriflunomide or safer and more

effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Ponvory® 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 with Conditions**

References

[1] Ponvory [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2021.