NEW DRUG APPROVAL

Brand Name	Ponvory™
Generic Name	ponesimod
Drug Manufacturer	Janssen Pharmaceutical Companies

New Drug Approval

FDA Approval Date: March 18, 2021

Review Designation: Standard

Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA) 213498

Dispensing Restrictions: Speciality Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system. Relapsing-remitting MS (RRMS) is the most common disease course and is characterized by periods of worsening neurologic symptoms ("relapses") followed by partial or complete recovery. Incomplete recovery from relapses may contribute to worsening neurologic function ("disability progression"). Over time, RRMS may transition to secondary progressive MS (SPMS). SPMS is characterized by irreversible disability progression that occurs in the absence of, or independent of, relapses.

About 400,000 Americans have MS, although this may be an underestimate. The disease affects about three times as many women as men and some patient groups, such as African Americans, experience a more rapid and severe clinical course. Our review looks at two types of multiple sclerosis: relapsing-remitting (RRMS) and primary-progressive (PPMS). RRMS affects about 85-90% of patients with MS, while PPMS affects about 10-15%. Patients with RRMS, experience periodic relapses in symptoms which may improve with treatment, while those with PPMS experience steadily worsening symptoms.

Nearly 1 million people are living with MS in the United States, with most people diagnosed between 20 and 50 years of age. The average person in the United States has about a 1-in-750 chance of developing MS. MS is at least 2 to 3 times more common in women than in men. In general, MS is more common in areas farthest from the equator. However, prevalence rates may differ significantly among groups living in the same geographic area regardless of distance from the equator.

Efficacy

The efficacy of Ponvory™ was demonstrated in Study 1, a randomized, double-blind, parallel group, active-controlled superiority study in patients with relapsing forms of MS. The efficacy results for Study 1 are presented in below Table:

Endpoints	**PONVORY 20 mg** N =567	**Teriflunomide 14 mg** N =566
Clinical Endpoints		
Annualized Relapse Rate[a]	0.202	0.290
Relative reduction	30.5% (p=0.0003)	
Percentage of patients without relapse[b]	70.7%	60.6%
Proportion of Patients with 3-month Confirmed Disability Progression[c]	10.8%	13.2%
Hazard Ratio[d]	0.83 (p=0.29)[e]	
MRI Endpoints[b, f]		
Mean number of new or enlarging T2 hyperintense lesions per year	1.40	3.16
Relative reduction	55.7% (p <.0001)	
Mean number of T1 Gd-enhancing lesions per MRI	0.18	0.43
Relative reduction	58.5% (p <.0001)	

All analyses are based on the full analysis set (FAS), which includes all randomized patients. N refers to the number of patients included in the FAS, per treatment group.

[a] Defined as confirmed relapses per year through the study period (Negative binomial regression model with stratification variables (EDSS ≤ 3.5 versus EDSS > 3.5; non-steroid treatment for MS within last 2 years prior to randomization [Yes/No]) and the number of relapses in the year prior to study entry (<=1, >=2) as covariates)

[b] Over the study period of approximately 108 weeks

[c] Disability progression defined as 1.5-point increase in EDSS for patients with a baseline EDSS score of 0, 1.0-point increase in EDSS for patients with a baseline EDSS score of 1.0 to 5.0, or 0.5-point increase in EDSS for patients with a baseline EDSS score at least 5.5 confirmed 3 months later. Proportion of patients with 3-month confirmed disability progression refers to Kaplan-Meier estimates at Week 108.

[d] Defined as time to 3 months confirmed disability progression through the study period (Stratified Cox proportional hazard model, p-value based on the stratified log rank test)

[e] Not statistically significant

[f] Cumulative number of combined unique active lesions (CUALs), defined as new or enlarging T2 lesions or Gd-enhancing T1 lesions (without double counting), mean lesions per year were 1.41 on ponesimod 20 mg (N=539), and 3.16 on teriflunomide 14 mg (N=536), a relative reduction of 56% (p<0.0001).

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Safety

ADVERSE EVENTS

Most common adverse reactions (incidence at least 10%) are upper respiratory tract infection, hepatic transaminase elevation, and hypertension.

WARNINGS & PRECAUTIONS

- Infections: Ponvory™ may increase the risk of infections. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Do not start Ponvory™ in patients with active infection.
- Bradyarrhythmia and Atrioventricular Conduction Delays: Ponvory™ may result in a transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for pre-existing cardiac conduction abnormalities before starting Ponvory™. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate.
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating Ponvory™.
- Increased Blood Pressure (BP): Monitor BP during treatment.
- Cutaneous Malignancies: Periodic skin examination is recommended.
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 1 week after stopping Ponvory™.
- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking Ponvory™. Diabetes mellitus and uveitis increase the risk.

CONTRAINDICATIONS

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

Clinical Pharmacology

MECHANISMS OF ACTION

Ponesimod 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 unknown but may involve reduction of lymphocyte migration into the central nervous system.

Dose & Administration

ADULTS

The recommended maintenance dosage is 20 mg taken orally once daily.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustments are needed.

HEPATIC IMPAIRMENT

Mild hepatic impairment (Child-Pugh class A): No dosage adjustments are needed.

Moderate or severe hepatic impairment (Child-Pugh class B or C): Use is not recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg