Drug Monograph

Drug Name: **Ponvory™ (ponesimod) Tablets**
Drug Class: **CNS: Multiple Sclerosis, Oral Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Ponvory is available as 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg tablets.
Manufacturer:	Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560.
Summary of Findings:	The efficacy of Ponvory was established in a multicenter, randomized, double-blind, parallel group, active-controlled superiority study of 1133 patients. Patients were randomized to receive either once daily Ponvory, beginning with a 14-day dose titration (N=567) or Aubagio (teriflunomide) 14 mg (N=566). The primary endpoint was the annualized relapse rate (ARR) over the study period. Additional outcome measures included: 1) the number of new Gd-enhancing T1 lesions from baseline to Week 108, 2) the number of new or enlarging T2 lesions (without double-counting of lesions) from baseline to Week 108, and 3) the time to 3-month and 6-month confirmed disability progression. The ARR was statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio 14 mg. The number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio 14 mg. There was no statistically significant difference in the 3-month and 6-month confirmed disability outcomes between Ponvory- and Aubagio 14 mg-treated patients over 108 weeks.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Multiple sclerosis (MS) is a disease of unknown etiology characterized by central nervous system (CNS) demyelination and axonal damage. A recent study launched and supported by the National MS Society estimates that in 2017, nearly 1 million people were living with MS in the United States. This estimation is more than twice the previously reported number from a national study in 1975. Diagnosis requires evidence of dissemination of lesions over time and in multiple parts of the CNS and/or optic nerve, and is made primarily on the basis of clinical symptoms and examination. MS is usually diagnosed between the ages of 15 and 45 years. Women are afflicted more than men by the ratio of 2:1. MS occurs more frequently in whites of Scandinavian ancestry that in other ethnic groups. Diagnostic criteria also allow for the use of magnetic resonance imaging (MRI), spinal fluid evaluation, optical coherence tomography, and evoked potentials. Exacerbations or relapses of MS can be disabling and are usually treated with high dose glucocorticoids. Treatment of relapsing-remitting multiple sclerosis (RRMS) with disease-modifying therapys (DMTs) can reduce annual relapse rate, lessen severity of relapses, slow progression of changes on MRI scans, slow progression of disability, slow cognitive decline, reduce the likelihood developing a second attack after a first clinically isolated syndrome (CIS) consistent with MS. In most cases, treatment with DMTs should begin promptly after the diagnosis of RRMS, or after a CIS if the brain MRI is suggestive of high risk of further attacks. Natalizumab and other choices that have been associated with problematic adverse events should be reserved for those patients who have failed one or more standard therapies and those with poor prognostic signs. The definition of treatment inadequacy for RRMS remains unclear, and therapy changes after “treatment failure” should be individualized. Patients suffering with MS frequently have symptoms such as spasticity, bladder dysfunction, fatigue, neuropathic pain, cognitive dysfunction, and depression that can require treatment. Patients must be counseled that DMTs will not relieve these symptoms.

Dosage Form [3]

Ponvory is available as 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg tablets.

Manufacturer [3]

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560.

Indication(s) [3]

Ponvory is indicated for the treatment of relapsing forms of MS, to include CIS, RRMS, and active secondary progressive disease (SPMS), in adults.

Clinical Efficacy [3,4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Ponvory is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to the S1P receptor 1. It blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which Ponvory exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Pharmacokinetics:

Absorption	t_{max}: 2 to 4 hours; Bioavailability: 84%
Metabolism	Ponesimod to M13 inactive metabolite: combination of non-CYP450 enzymes Ponesimod to M12 inactive metabolite: CYP2J2, CYP3A4, CYP3A5, CYPF3A, CYP4F12 and non-CYP450 enzymes Ponesimod also undergoes glucuronidation (mainly UGT1A1 and UGT2B7)
Excretion	Feces: 57-80%; Urine 10-18%
Half-life	33 hours

Clinical Trials Experience

STUDY 1 DESIGN NCT02425644	Multicenter, randomized, double-blind, parallel group, active-controlled, Phase 3, superiority study (N=1133)
INCLUSION CRITERIA	• Age 18-55 years • Established diagnosis of MS McDonald 2019 with relapsing course from onset (i.e., RRMS and SPMS with superimposed relapses) • Active disease evidenced by one or more MS attacks with onset within the period of 12 to 1 months prior to randomization, or by two or more MS attacks with onset within the 24 to 1 months prior to randomization, or with one or more Gd+ lesion(s) of the brain on an MRI performed within 6 months prior to randomization • Ambulatory patients (EDSS score of up to 5.5 inclusive) • May be treatment-naïve or previously treated with MS disease modifying therapy
EXCLUSION CRITERIA	• Subjects with significant medical conditions or therapies for such conditions (e.g., cardiovascular, pulmonary, immunological, hepatic, ophthalmological conditions) or lactating or pregnant women • Subjects with contraindications to MRI or with clinically relevant medical or surgical conditions that, in the opinion of the investigator, would put the subject at risk by participating in the study • Patients with primary progressive MS
TREATMENT REGIMEN	Patients were randomized to receive either once daily Ponvory, beginning with a 14-day dose titration (N=567) or Aubagio (teriflunomide) 14 mg (N=566).

<table>
<tr><td></td><td>Neurological evaluations 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.</td></tr>
<tr><td>RESULTS</td><td>The primary endpoint was the annualized relapse rate (ARR) over the study period.
Additional outcome measures included: 1) the number of new Gd-enhancing T1 lesions from baseline to Week 108, 2) the number of new or enlarging T2 lesions (without double-counting of lesions) from baseline to Week 108, and 3) the time to 3-month and 6-month confirmed disability progression (defined as an increase of at least 1.5 in EDSS for patients with a baseline EDSS score of 0, or an increase of at least 1.0 in EDSS for patients with a baseline score of 1.0 to 5.0, or an increase of at least 0.5 EDSS for patients with a baseline EDSS score of at least 5.5, which was confirmed after 3 months and 6 months).

<table>
<tr><th></th><th>Ponvory 20 mg
(N=567)</th><th>Aubagio 14 mg
(N=566)</th></tr>
<tr><td>Primary Endpoint</td><td></td><td></td></tr>
<tr><td>Annualized Relapse Rate</td><td>0.202</td><td>0.290</td></tr>
<tr><td>Relative reduction</td><td colspan="2">30.5% (p=0.0003)</td></tr>
<tr><td>% of patients without relapse</td><td>70.7%</td><td>60.6%</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Secondary Endpoints</td><td></td><td></td></tr>
<tr><td>Proportion of patients with 3-month confirmed disability progression</td><td>10.8%</td><td>13.2%</td></tr>
<tr><td>Hazard ratio</td><td colspan="2">0.83 (p=0.29)</td></tr>
<tr><td>Mean number of new of enlarging T2 hyperintense lesions per year</td><td>1.40</td><td>3.16</td></tr>
<tr><td>Relative reduction</td><td colspan="2">55.7% (p<0.0001)</td></tr>
<tr><td>Mean number of T1 Gd-enhancing lesion per MRI</td><td>0.18</td><td>0.43</td></tr>
<tr><td>Relative reduction</td><td colspan="2">58.5% (p<0.0001)</td></tr>
</table>

The ARR was statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio 14 mg. The number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio 14 mg. There was no statistically significant difference in the 3-month and 6-month confirmed disability outcomes between Ponvory- and Aubagio 14 mg-treated patients over 108 weeks.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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Abbreviations: EDSS=Expanded Disability Status Scale; Gd=gadolinium-enhancing; MRI=magnetic resonance imaging

Contraindications [3,4]

- 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.

Warnings and Precautions [3,4]

- **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 preexisting 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.

Adverse Effects [3,4]

Most common, ≥ 5%	Ponvory 20 mg (n =565) %	Aubagio 14 mg (N=566) %
Upper respiratory tract infection	37	34
Hepatic transaminase elevation	23	12
Hypertension	10	9
Urinary tract infection	6	5
Dyspnea	5	1
Dizziness	5	3

Drug Interactions [3,4]

- **Vaccines**: Avoid live attenuated vaccines during and for up to 1-2 weeks after treatment with Ponvory.
- **Strong CYP3A4 and UGT1A1 Inducers**: Coadministration with Ponvory is not recommended (e.g., carbamazepine, rifampin, phenytoin).

Dosage and Administration [3,4]

- Before initiation of treatment with Ponvory, assess the following: CBC, cardiac function (ECG), liver function tests, ophthalmic evaluation, current or prior medication with immune system effects, vaccination status/titer of varicella zoster virus (VZV).
- Titration is required for treatment initiation.

Titration Day	Daily Dose
Days 1 and 2	2 mg
Days 3 and 4	3 mg
Days 5 and 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Days 12, 13, and 14	10 mg
Maintenance	**Daily Dose**
Day 15 and thereafter	20 mg

- The recommended maintenance dosage is 20 mg orally once daily with or without food.
- 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. Monitor patients for signs and symptoms of bradycardia for 4 hours after the first dose in a setting with resources to appropriately manage symptomatic bradycardia. At minimum measure hourly pulse and blood pressure. Obtain an ECG in these patients prior to dosing and at the end of the 4-hour observation period.
- If any of the following abnormalities 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 45 beats per minute (bpm)
    - The heart rate 4 hours post-dose is at the lowest value post-dose, suggesting that the maximum pharmacodynamics effect on the heart rate 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 greater than or equal to 500 msec, initiate appropriate management, begin continuous ECG monitoring and continue monitoring until the 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 during treatment initiation, if treatment with Ponvory is considered in patients:
    - With some preexisting heart and cerebrovascular conditions
    - With a prolonged QT_c 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 torsades de pointes.
    - Receiving concurrent therapy with drugs that slow heart rate or AV conduction.
- If more than 4 consecutive doses are missed, treatment should be restarted with Day 1 of titration schedule.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Ponesimod	Ponvory™	Janssen Pharmaceuticals	20 mg orally once daily	$8,083.50
Fingolimod	Gilenya®	Novartis Pharmaceuticals	0.5 mg orally once daily	$9,095.34
Siponimod	Mayzent®	Novartis Pharmaceuticals	1 or 2 mg orally once daily (based on genotype)	$4,028.87-$8,057.74
Ozanimod	Zeposia®	Celgene Corp Division of BMS	0.92 mg orally once daily	$7,386.57

** Wholesale Acquisition Cost

Conclusion

Ponvory is the fourth S1P receptor modulator for MS and was approved by the FDA March 18, 2021. It suppresses the immune system by sequestering circulating lymphocytes into secondary lymphoid organs and reduces infiltration of T lymphocytes and macrophages into the CNS. This action may produce some neuroprotective effects in patients with relapsing forms of MS. The efficacy of Ponvory was established in a multicenter, randomized, active-controlled trial versus Aubagio 14 mg daily. Primary endpoint was designated as the annualized relapse rate over the 108 week treatment period. The ARR was statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio. The number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in patients treated with Ponvory than in patients who received Aubagio 14 mg, and no statistically significant difference in the 3-month and 6-month confirmed disability outcomes between Ponvory- and Aubagio 14 mg-treated patients over 108 weeks, which were included as secondary or additional endpoints. The recommended dose is 20 mg daily after a 14-day titration period which begins with a monitored first-dose due to the risk of bradycardia, bradyarrhythmia, or conduction related symptoms in certain patients. Ponvory is contraindicated in patients with a recent cerebrovascular event and patients with specific types of heart block and sick sinus syndrome. The most common adverse reactions include upper respiratory tract infection, hepatic transaminase elevation, hypertension, urinary tract infection, dyspnea, and dizziness.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) Wallin M, Culpepper W, et al. (2019). The prevalence of MS in the United States. *Neuro.* 92 (10) e1029-e1040; DOI: 10.1212/WNL.0000000000007035.
2) Rae-Grant A, Day GS, Marrie, RA, et al. Comprehensive Systematic Review Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis Report of the Guideline Development, Dissemination, and Implementation Subcommittee of American Academy of Neurology. *Neuro*. Oct 2019 93(17) 769; DOI: 10.1212/WNL0000000000008374.
3) Ponvory [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2021.
4) Clinical Pharmacology [drug reference database]. Available at: https://secure.ipdanalytics.com/User/Home?ReturnUrl=%2FUser%2F&SkipConfirmProfile=Falsehttps:www.clinicalkey.com/pharmacology/. Accessed April 20, 2021.

5) Ponvory [new drug review]. IPD Analytics. Available at:
6) Kappos L, Fox RJ, Burcklen M, et al. Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. JAMA Neurol. 2021 Mar 29:e210405. doi: 10.1001/jamaneurol.2021.0405.
7) UpToDate [drug reference database]. Available at: https://www.uptodate.com/contents/society-guideline-links-multiple-sclerosis-and-related-disorders?search=sphingosine%201%20receptor%20modulators&topicRef=129091&source=see_link#H806669904

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