Ponesimod (PONVORY)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Sphingosine 1-phosphate receptor modulator, purportedly selective for $S1P_1$ subtype

Indication(s) Under Review in This Document

- Relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (aSPMS) in adults

Dosage Form(s) Under Review

- Oral tablets to be taken once daily
    - Starter pack (includes 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, and 10mg tablets)
    - 20mg tablets

Clinical Evidence Summary

Efficacy Considerations

- The initial trial involving clinical outcomes in an MS population was a Phase 2b trial[1]
- The pivotal trial for ponesimod approval was a randomized, controlled Phase 3 trial (OPTIMUM) [2]. This trial supports the safety and efficacy of ponesimod for the treatment of RMS.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Design	Key Inclusion/Exclusion	Endpoints/Results
Phase 2b	24 week Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study of ponesimod in the treatment of RRMS N=464 Treatment: ponesimod 10mg, 20mg, or 40mg PO qday or placebo. Patients randomized to ponesimod 20mg or 40mg were titrated starting at 10mg/d.	Inclusion: Patients aged 18-55 with RRMS (per 2005 McDonald criteria), baseline Expanded Disability Status Scale (EDSS) 0.5-5, active disease (defined by 1 or more documented relapse within 12 months, or 2 or more documented relapses within 24 months, or 1 or more Gd+ T1 lesion on MRI at screening) Exclusion: Corticosteroids within 30 days, IFN β or glatiramer within 3 months of randomization. Restrictions on immunosuppressants within 3 months or 6 months depending on the agent. Cyclophosphamide, mitoxantrone, cladribine, alemtuzumab, or rituximab at any time	Primary endpoint: Cumulative new T1-weighted Gd+ lesions Ponesimod 10mg: 3.5, 43% reduction RR 0.57 (95% CI: 0.337-0.952), p=0.0318 20mg: 1.1, 83% reduction RR: 0.17 (95% CI: 0.100-0.289), p<0.0001 40mg: 1.4, 77% reduction RR 0.23 (95% CI: 0.133-0.384), p>0.0001 placebo: 6.2 Secondary endpoints: Annualized relapse rate (ARR) Ponesimod 10mg: 0.33, p=0.1619 20mg: 0.42, p+0.4420 40mg: 0.25, p=0.0363 Placebo: 0.53 Time to first confirmed relapse within 24 weeks Ponesimod 10mg hazard ratio (HR) 0.64 (95% CI: 0.33-1.22) 20mg HR 0.79 (95% CI: 0.43-1.45) 40mg HR 0.42 (95% CI: 0.20-0.87) Placebo
OPTIMUM	108 week Phase 3, multicenter,	Inclusion: Patients aged 18-55 with RMS	Primary Endpoint: ARR

	randomized, double-blind, active-comparator, superiority safety and efficacy study of ponesimod in the treatment of RMS N=1133 Treatment: ponesimod 20mg PO qday with 14 day up-titration or teriflunomide 14mg PO qday. Patients randomized to ponesimod were titrated over 14 days starting at 2mg/d.	(per 2010 McDonald criteria), EDSS 0-5.5, recent clinical or MRI activity, treatment-naïve or previously treated with IFN β-1a, IFN β-1b, glatiramer, natalizumab, or dimethyl fumarate <u>Exclusion:</u> Progressive MS, significant medical conditions, pregnant or lactating, moderate or severe liver impairment, CrCl<30mL/min, relapse within 30d prior to baseline EDSS or randomization, active infection, hep B or C, HIV, negative VZV ab, history of malignancy or pre-cancerous skin lesions, macular edema Cardiac exclusions: HR<50 BPM, recent MI, class III or IV heart failure, hx of valvular heart disease or rhythm disorders, second-degree AV block Mobitz Type II or third-degree AV block, QTcF >470 (female), >450	Ponesimod 242 relapses , mean 0.202, teriflunomide 344 relapses, mean 0.290. Ratio rate 0.695 (99% CLs 0.536-0.902) p<0.001 <u>Secondary Endpoints:</u> Changes in the symptom domain of Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) at week 108 Ponesimod 0.01, teriflunomide 3.56. (95% CLs -5.83 to -1.32) p=0.002 Number of combined unique active lesions (CUALs) per year on MRI Ponesimod 1.405, teriflunomide 3.164. Ratio rate 0.444 (95% CLs 0.364-0.542) p<0.001 Time to 12-week and 24-week confirmed disability accumulation 12-week: Ponesimod 10.1%, teriflunomide 12.4%. HR 0.83 (95% CL 0.58-1.18) p=0.29. 24-week CDA rendered exploratory due to stopping formal testing procedure <u>Exploratory Endpoints:</u> Percentage change in brain volume Least-squares mean percentage chance ponesimod -0.91%, teriflunomide -1.25% No evidence of disease activity (NEDA-3 and NEDA-4) status NEDA-3: ponesimod 25.0%, teriflunomide 16.4% NEDA-4: ponesimod 11.4%, teriflunomide 6.5%

		(male), history of syncope associated with cardiac disorders Treatment with IFN β-1a, IFN β-1b, or glatiramer within 7 days, treatment with anti-arrhythmic or heart rate lowering therapy within 15 days, ACTH or corticosteroids, dimethyl fumarate, or live vaccine within 30 days, natalizumab or systemic immunosuppressant within 180 days, rituximab, ocrelizumab, or cladribine within 24 months, alemtuzumab, mitoxantrone, leflunomide, teriflunomide, fingolimod, ponesimod, or stem-cell transplant at any time	

OPTIMUM was the pivotal trial supporting the efficacy of ponesimod for treatment of RMS. It was a Phase 3, multicenter, randomized, double-blind, active-comparator, superiority, safety and efficacy study which compared ponesimod 20mg PO qday to teriflunomide 14mg PO qday. To minimize risk of

bradycardia, patients randomized to ponesimod were titrated starting at 2mg/d over 14 days to a target dose of 20mg/d. OPTIMUM enrolled 1133 patients at 162 centers. The treatment period was 108 weeks. Baseline demographics were well matched. The primary endpoint was annual relapse rate (ARR), calculated from number of confirmed relapses per patient year. The results were favorable with 242 confirmed relapses in the ponesimod group (mean ARR 0.202%) versus 344 (mean ARR 0.290%) for teriflunomide. This represents a 30.5% relative reduction in ARR (99% CL 0.536-0.902, p<0.001).

Secondary endpoints included change in the symptom domain of Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS), number of combined unique active lesions (CUAL) on MRI, and time to 12-week and 24-week disability accumulation. The FSIQ-RMS is a 77 point, patient-reported questionnaire addressing the impact of fatigue in RMS with a higher number indicating more fatigue. The mean difference in FSIQ-RMS score for the ponesimod group was an increase of 0.01 vs. 3.56 in the teriflunomide group. This was statistically significant (95% CLs -5.38 to -1.32, p = 0.002) but the clinical significance is not well established. The mean number of combined unique active lesions (CUALs) per year on MRI was 1.405 in the ponesimod group and 3.164 in the teriflunomide group which was statistically significant (ratio rate 0.444 (95% CLs 0.364-0.542, p<0.001). Time to 12-week confirmed disability accumulation (CDA) was not statistically different between groups. Time to 24-week CDA was rendered exploratory but was also not statistically different. The trial included some exploratory outcomes as well, including change in brain volume and no evidence of disease activity (NEDA-3 and NEDA-4 status).

These data indicate that ponesimod is an effective treatment for reducing clinical relapses and new MRI lesions, but do not indicate an effect on disability progression.

One important limitation of this study is that the population was almost entirely European and Caucasian so results may not be generalizable to the overall RMS population.

Safety Considerations

Safety Results from Clinical Trials:
In the Phase 2b trial, the following treatment-emergent adverse events (TEAEs) occurring more in ponesimod groups than placebo: anxiety, dizziness, dyspnea, increased transaminases, influenza, insomnia, and peripheral edema. The authors noted that dyspnea and peripheral edema AEs appear to be dose related. Dyspnea was commonly reported by patients on ponesimod: 9.3% of patients on 10mg, 16.7% of patients on 20mg and 31.9% of patients on 40mg. Of the placebo group, 6.6% of patients reported dyspnea. Seven patients in the ponesimod groups discontinued treatment due to dyspnea, six of which were in the 40mg treatment group. There was a total of 27 serious adverse events (SAEs) reported. Five of these were in the placebo group (4.1% of patients) and 22 were in ponesimod treatment groups (6.5% of patients). SAEs that occurred more than once include macular edema, second-degree AV block, and appendicitis. None were in the placebo group. There was a total of four cases of macular edema reported, one of which was in the placebo group.

Two cases of malignancy were reported: one breast cancer (ponesimod 10mg group) and one case of cervical carcinoma (placebo group). There were cardiac adverse events (AV block and bradycardia) associated with the first dose of ponesimod, which was 10mg in this study. All of these resolved without intervention, and none recurred.

In the OPTIMUM trial, the total number of reported TEAEs was similar between groups. By titrating ponesimod from an initial dose of 2mg/d, first-dose bradycardia and AV block were minimized. OPTIMUM reported an incidence of 2.1% of first-dose heart rate and rhythm AEs.
Common and noteworthy TEAEs included ALT increases (19.5% for ponesimod vs 9.4% teriflunomide), nasopharyngitis (19.3% vs 16.8%), headache (11.5% vs 12.7%), URI (10.6% vs 10.4%), HTN (8% vs 7.8%), UTI (5.7% vs 5.1%), dyspnea (5.3% 1.2%), and dizziness (5% vs 2.7%). The number of patients who discontinued treatment due to AEs in the ponesimod group was 8.7% compared to 6.0% in the teriflunomide group. The AEs responsible for the most treatment discontinuation in the ponesimod group was dyspnea, followed by ALT elevation and macular edema, then pregnancy and other hepatic enzyme elevation. Two patients discontinued treatment due to lymphopenia. There was a total of 49 (8.7%) reported SAEs in the ponesimod group compared to 46 (8.1%) in the teriflunomide group. No clusters of serious events were identified.

- **Contraindications:**
    - Recent myocardial infarction, unstable angina, stroke or TIA, decompensated heart failure requiring hospitalization, or Class III/IV HF
    - Mobitz type II second-degree, third-degree AV block, sick sinus syndrome, or sino-atrial block, unless patient has functioning pacemaker
- **Warnings and precautions**:
  Infections and lymphocytopenia – Ponesimod may increase risk of infection. Do not initiate ponesimod in patients with active infection. Check CBC and ZVZ antibodies before treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Ponesimod sequesters lymphocytes in lymphoid tissues which reduces peripheral lymphocyte counts by 30-40% of baseline. In the OPTIMUM trial, 3.2% of patients had lymphocytes less than $0.2x10^9$/L. Lymphocyte counts returned to normal in most patients within 1 week of discontinuing ponesimod. The number of herpetic infections in the ponesimod group was 4.8% which was similar to the teriflunomide group. Cryptococcal infections and progressive multifocal leukoencephalopathy (PML) have been reported with other S1P receptor modulators.
  Bradycardia and AV conduction delays – Ponesimod may result in transient bradycardia; titration is required at initiation. Check ECG to assess for preexisting cardiac conduction abnormalities before treatment initiation. Avoid use with other medications which decrease heart rate. In the OPTIMUM trial, 5.8% of patients on ponesimod experienced bradycardia compared to 1.6% on teriflunomide. This was most pronounced after the first dose, with a mean decrease of 6 BPM. All resolved without intervention. Three patients with a baseline HR less than 55 BPM had asymptomatic bradycardia with HR ≤ 40 BPM after the first dose. There were similar findings for first dose-related first-degree AV conduction delays (3.4% of patients on ponesimod vs 2.2% of patients on teriflunomide. There were no reports of second- or third-degree AV block.

Missed dose during treatment – Patients should re-titrate ponesimod if they miss more than three consecutive doses.
Pulmonary – may cause a decline in pulmonary function. Check PFTs if clinically indicated. Use with caution in patients with a history of severe respiratory disease. A reduction in percent predicted FEV_1 was 8.3% in patients on ponesimod compared to 4.4% of patients on teriflunomide. Seven patients discontinued ponesimod due to dyspnea in the OPTIMUM trial. It is unclear if these pulmonary changes are reversible.
Liver injury – Check LFTs before treatment initiation. Discontinue if significant liver injury (two times the upper limit of normal range (2N) in serum alanine aminotransferase (ALT) or conjugated bilirubin, or a combined increase of aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin, provided one of them is above 2N) is confirmed. In the OPTIMUM trial 4.6% of patients treated with ponesimod developed ALT 5 times ULN compared to 2.5% of patients on teriflunomide. Of patients whose ALT elevated to 3 times ULN (17.3% vs 8.3%), the majority continued treatment and elevations resolved within two to four weeks.
Increased BP – Monitor BP during treatment. In the OPTIMUM trial, patients on ponesimod experienced elevations in BP with an average increase of 2.9mmHg/2.8mmHg compared to 2.8mmHg/3.1mmHg for patients on teriflunomide. These elevations persisted.
Cutaneous malignancy – Periodic skin examination is recommended as various malignancies have been reported in patients on ponesimod and other S1P receptor modulators.
Fetal risk – Patients of childbearing potential should use effective contraception during treatment and for 1 week after discontinuation. Animal studies have shown adverse effects on developing fetuses from ponesimod at clinically relevant maternal exposure levels, therefore ponesimod should be avoided during pregnancy. Also, ponesimod has been detected in plasma of offspring, so risks and benefits should be carefully considered for lactating patients.
Macular edema - Recommend ophthalmic evaluation prior to treatment and if any vision changes. Diabetes and uveitis increase this risk, so patients with a history of either should undergo regular ophthalmic evaluations including examination of the fundus and macula.
Posterior reversible encephalopathy syndrome (PRES) – PRES has been rarely reported during treatment with other S1P receptor modulators, so caution is advised.
Severe increase in disability after stopping ponesimod – Disease rebound has been reported after discontinuation of S1P receptor modulators, therefore caution is advised when discontinuing ponesimod.

- **Adverse reactions**
  Common - The following AEs were reported at an incidence of at least 10%: upper respiratory tract infection, transaminase elevation, and hypertension.
  Serious Adverse events / Discontinuation - There was an overall low frequency of AEs which lead to treatment discontinuation in ponesimod trials.

Other Considerations

Geriatric use – Patients aged 65 years and older have been excluded from clinical trials of ponesimod, therefore caution is advised in this population.

Hepatic impairment – Ponesimod should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh class A)

Other Therapeutic Options

Alternative S1P receptor modulators for treatment of multiple sclerosis are listed in table 2

Table 2 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Ponesimod	TBD	Treatment of relapsing forms of MS, to include CIS, RRMS, and aSPMS	Contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, 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, or sino-atrial block, unless patient has a functioning pacemaker
Fingolimod	F	Treatment of relapsing forms of MS to include CIS, RRMS, and aSPMS in patients ≥ 10 years old	Requires 6 hour observation period after the first dose is administered. The development of macular edema, melanomas, basal cell carcinomas and infections may occur with fingolimod therapy. Laboratory changes reported with fingolimod include a decrease in peripheral blood lymphocyte counts and elevations in liver function tests
Siponimod	NF	Treatment of relapsing forms of MS, to include CIS, RRMS, and aSPMS in adults	Contraindicated in patients with a CYP2C9*3/*3 genotype, patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, 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
Ozanimod	NF	Treatment of relapsing forms of MS to include CIS, RRMS, and aSPMS in adults	Has active metabolite which inhibits MAO-B, so DDIs with opioids, serotonergic medications, and sympathomimetic medications. Contraindicated in severe untreated sleep apnea, or concomitant use of MAO-I, in patients who 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 or third degree atrioventricular block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker.

Projected Place in Therapy

- Ponesimod showed a statistically better annualized relapse rate (ARR) (a 30.5% relative reduction) and fewer combined unique active lesions (CUALs) on MRI per year compared to teriflunomide.
- A statistical difference between ponesimod and teriflunomide was shown for the symptom domain of Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) but this small difference is likely not clinically meaningful.
- Time to 12-week disability differences between groups did not reach statistical significance. Because of this and that formal testing had stopped, the time to 24-week disability analysis was rendered exploratory; it was also not statistically different.
- Based on the mean reduction in relapses of patients treated with ponesimod compared to teriflunomide, it can be calculated that 12 patients per year would need to be treated with ponesimod rather than teriflunomide in order to prevent one relapse.
- The safety profile of ponesimod is largely similar to other approved S1P receptor modulating agents.
- There have been no direct comparisons between ponesimod and other S1P receptor modulating agents, however its efficacy is expected to be similar. In patients with low cardiac risk, first dose monitoring is not required for ponesimod which is an advantage over fingolimod. A disadvantage is that ponesimod has a much shorter elimination half-life than fingolimod and requires repeat dose titration if more than 3 consecutive doses are missed.
- Ponesimod does not have any additional concerning drug interactions beyond those which have been described for the class. This is an advantage over ozanimod which has several important drug interactions and food restrictions.
- Siponimod requires genotype testing prior to therapy initiation; ponesimod does not.
- There is a substantial cost difference between the agents which should be considered in selection of therapy.

References

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