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Pondering Ponvory® (Ponesimod): Preparing for Multiple Sclerosis

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Multiple Sclerosis (MS) is a neurological disease of the central nervous system that attacks the myelinated axons, destroying the myelin.[1] MS may present with varying severity from initial episodes of reversible neurological deficits; such as spasticity, paresthesia (numbness/tingling), dysesthesia (burning or "pins and needles"), diplopia, ataxia, vertigo, and urinary disturbances to disabling and progressive neurological deterioration over time resulting in cognitive and physical incapacitation as communication between axons are disrupted.[1]

Multiple sclerosis is an unpredictable disease, and most people experience their first symptoms between the ages of 20 and 40.[2] The etiology of MS is unclear, however it appears to involve genetic factors and nongenetic triggers, such as viruses, metabolism, or environmental factors that together illicit a self-sustaining autoimmune disorder leading to recurrent immune attacks on the central nervous system (CNS).[1] Biological females of Northern European descent are twice as likely as biological males to develop MS.[1] Approximately 250,000 to 350,000 patients in the U.S. have been diagnosed MS, and 50% of patients will require assistive devices to walk within 15 years after the onset of the disease due to extreme weakness in the extremities and difficulty with balance and coordination.[1,2]

There are four major categories of MS based on the course of the disease. One category is relapsing-remitting MS (RR-MS) and is the most common form, affecting 85% of MS patients.[1] It is characterized by flare-ups of symptoms followed by periods of remission. Secondary progressive MS (SP-MS) can develop in patients with RR-MS, but the disease course continues to worsen with or without periods of remission or leveling-off symptom severity. A third category is primary progressive MS (PP-MS), which affects approximately 10% of MS patients and is characterized by symptoms that worsen gradually from the beginning of diagnosis. These individuals experience no relapses or remissions, and this form tends to be more resistant to the drugs that are currently available to treat MS. The final category to note is progressive-relapsing MS (PR-MS), which is the rarest form affecting fewer than 5% of patients. It is progressive from diagnosis with intermittent flares of worsening symptoms and no periods of remission.[1]

Clinical manifestations of MS involve the motor, sensory, visual, and autonomic systems. Few of the clinical features are disease specific, but two characteristic signs are the Lhermitte's symptom and the Uhthoff phenomenon. Lhermitte's symptom is a shock-like sensation that travels down the spine, arms, and legs, and sometimes the trunk of the body with flexion of the neck.[3] The Uhthoff phenomenon is a transient worsening of signs and symptoms when core body temperature increases after exercise or hot baths, most often associated with optic neuritis and temporary worsening of vision.[4]

There are no specific diagnostic tests for MS and the diagnosis is determined by ruling out other conditions that might produce similar signs and symptoms.[5] The 2017 Revised McDonald Criteria published by the International Panel on the Diagnosis of Multiple Sclerosis, includes guidelines for using magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis to speed the diagnostic process.[6] Lesions in the brain are detected by MRI and are likely caused by inflammation and/or demyelination. In some circumstances, the presence of oligoclonal bands in a person's CSF analysis can be used instead of dissemination of damage in time to confirm the MS diagnosis.[6]

Disease-modifying therapies (DMTs) are essential therapeutics for comprehensive MS care which are proven to be effective in reducing the frequency and severity of clinical relapses, reducing the development of new lesions within the brain and spinal cord, and slowing down the accumulation of disability. These medications generally do not improve everyday symptoms of the disease but can help prevent damage to the CNS and slow progression.[7] Injectable DMTs interferon beta-1a, interferon beta-1b, immunomodulators glatiramer acetate and pegylated interferon beta-1a, and ofatumumab a monoclonal antibody, are used for treating MS. Oral therapies available include teriflunomide, fingolimod, siponimod, ozanimod, cladribine, dimethyl fumarate and diroximel fumarate. The intravenous infusion treatments are the humanized monoclonal antibodies alemtuzumab, ocrelizumab, and natalizumab, and mitoxantrone an anthracenedione.[7]

There is no uniform algorithm for selecting any of the above DMT options however one approach is starting treatment early with a high efficacy DMT, such as the monoclonal antibodies.[8]

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Other clinicians may start with low-risk therapies, such as the interferons or glatiramer acetate for patients with lower disease burden or risk averse.[8] The American Academy of Neurology (AAN) 2018 guidelines for disease-modifying therapies for adults with MS state that clinicians should prescribe alemtuzumab, natalizumab, or fingolimod for patients with highly active MS characterized by relapsing activity and new lesions on MRI.[9] For patients with relapsing forms of MS who do not have access to approved DMTs, the 2018 guidelines stated that clinicians may recommend azathioprine or cladribine.[9] However, in March 2019, the Food and Drug Administration (FDA) approved oral cladribine for relapsing and secondary progressive forms of MS.[10] Cladribine is highly efficacious but due to its safety profile, it is only used in patients that have had inadequate response to other DMTs.[11] Azathioprine has low efficacy in relapsing forms of MS but continues to be prescribed off-label.[9]

In March 2021, the U.S. FDA granted approval for Ponvory® (ponesimod), an oral treatment used for adults with relapsing multiple sclerosis.[12,13] This article will discuss ponesimod's pharmacology, pharmacokinetics, pharmacodynamics, dosing and administration, evidence on safety and efficacy, and its clinical implications.

Pharmacology

Mechanism of Action

In autoimmune diseases, such as MS, the immune system recognizes self-antigens. A vicious cycle of self-antigen recognition perpetuates in lymph nodes, followed by T cell expansion, lymph node exit, and migration to damaged tissue expressing the self-antigen drives the lymphocyte-mediated inflammation.[14] In order for immune cells to exit the lymph nodes it has to pass through an endothelial barrier mediated by sphingosine 1-phosphate (S1P).[14] Ponesimod is a selective, reversible, orally active S1P receptor agonist that binds with high affinity to S1P receptor 1 (S1P-R1).[15] This receptor is one of five G-protein-coupled S1P receptors and mediates lymphocyte exit.[15] Nonselective S1P receptor agonists inhibit lymphocytes into the peripheral blood leading to a reduction in serum lymphocyte count.[14] Following endogenous S1P-mediated receptor activation, the S1P-R1 is internalized.[16] This internalization is quickly reversible, due in part to the actions of intracellular S1P-processing enzymes. The synthetic S1P-R1 modulators also activate the receptor and the internalization mechanism; they are, however, not readily cleared intracellularly, and result in long-lasting internalization of S1P-R1. The consequent loss of S1P-R1 signaling is thought to be responsible for the sustained inhibition of the exit of lymphocytes from lymphoid organs and a sustained lymphocyte count decrease in peripheral blood.[15]

Pharmacokinetics

The maximum serum concentration (C_{max}) and area under the curve (AUC) of ponesimod increase proportionally to dose.[16,17] Steady state levels are approximately 2.0-2.6 times greater than a single dose and achieved after three days of administration of the maintenance dose.[16] Time to C_{max} is 2-4 hours post dose with a bioavailability of 84% for a 10 mg dose. Food does not have a clinically relevant effect on the pharmacokinetics. Ponesimod is highly protein bound (>99%) with a steady state volume of distribution (Vd) of 160 liters. Animal studies showed that ponesimod was able to readily cross the blood brain barrier. Metabolism to M13 occurs primarily through a combination of CYP450 enzymatic activities where as CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12 and non-CYP450 enzymes catalyze the oxidation of ponesimod to M12. It also undergoes direct glucuronidation by UGT1A1 and UGT2B7. Ponesimod is eliminated with a mean half-life varying between 21.7 and 33.4 hours.[17] From the oral dose, 57-80% was recovered in the feces with 16% unchanged as ponesimod and 10-18% was in urine as unchanged ponesimod.[16] A summary of ponesimod's pharmacokinetic parameters can be found on **Table 1**.

Table 1 | Select Ponesimod Pharmacokinetics[16,17]

Absorption	
T_{max}[a]	2-4 hours
SS_t[b]	3 days
Distribution	
Vd[c]	160 L
Protein Binding	≥ 99%
Metabolism	
CYP450 enzymes, Oxidation (UGT1A1,UGT2B7)	
Elimination	
$T_{1/2}$[d]	33 hours
Fecal	16%
Urine	10-18%

[a]Time to maximum concentration; [b]Time to steady state; [c]Volume of distribution; [d]Half-life

Clinical Trials

The following section will highlight the results of ponesimod's phase II-III clinical trials and will be summarized on **Table 2.** These trials were pivotal in the FDA's decision of approving ponesimod for the treatment of relapsing MS.

Phase II Trial—Olsson et al.[18]

In the trial NCT01006265, the efficacy and safety of oral ponesimod in the treatment of relapsing multiple sclerosis (R-MS) was evaluated. This trial was a randomized, double-blind, placebo-controlled, dose-finding phase IIb trial.[18] A total of 464 participants 18-55 years of age were randomized to receive oral ponesimod 10mg (n=108), 20mg (n=114), or 40mg (n=119) or placebo (n=121) for 24 weeks. The primary endpoint was the cumulative number of new T1 gadolinium enhanced (T1 Gd+) lesions per patient recorded every four weeks from weeks 12 to 24 after study drug initiation. Gadolinium is a chemical compound given during MRI scans to show areas of inflammation indicating active lesions and disruption of the blood of the blood brain barrier. Secondary endpoints were the annualized relapse rate (ARR) and time to first confirmed relapse. A confirmed relapse is defined as a new, worsening, or recurrent neurological symptom that occurred 30 days after a preceding relapse, lasted at least 24 hours, in the absence of fever or infection, and accompanied a documented decrease in Expanded Disability Status Scale (EDSS) from a previous clinical assessment. All participants randomized to ponesimod initially received ponesimod 10 mg on Days 1–7. On Day 8, participants doses were up titrated to stay on 10 mg daily or increased to 20 mg daily. On Day 15, participants randomized to receive ponesimod 40 mg were up titrated to the 40 mg dose or continued their previous dose.[18]

The primary efficacy endpoint of mean cumulative number of new T1 Gd+ lesions at weeks 12–24 showed significant dose-

dependent reductions in each ponesimod group compared with the placebo group.[18] The cumulative number of new T1 Gd+ lesions was 3.5 [rate ratio (RR) 0.57, 95% confidence interval (CI) 0.337-0.952; p=0.0318)] with ponesimod 10 mg, 1.1 (RR 0.17, 95% CI 0.100-0.289; p<0.0001) with ponesimod 20 mg, 1.4(RR 0.23, 95% CI 0.133-0.384; p<0.0001) with ponesimod 40 mg, and 6.2 with placebo. The mean ARR was reduced in each ponesimod group compared with placebo by 37% (p=0.1619) with ponesimod 10 mg, by 21% (p=0.4420) with ponesimod 20 mg, and by 52% (p=0.0363) with ponesimod 40 mg. Ponesimod also proved effective in increasing the time to first confirmed relapse compared to placebo within 24 weeks. The risk of first confirmed relapse was reduced by 36% [hazard ratio (HR) 0.64, 95% CI 0.33 -1.22] in the ponesimod 10 mg group, by 21% (HR 0.79, 95% CI 0.43-1.45) in the ponesimod 20 mg group, and by 58% (HR 0.42, 95% CI 0.20-0.87) in the ponesimod 40 mg group compared with placebo. Mean lymphocyte reductions from baseline to week 24 were 50%, 65% and 69% for ponesimod 10, 20 and 40 mg, respectively, and 3% in the placebo group. Most adverse events (AE) were mild or moderate in intensity, and the proportions of patients who had ≥1 AE during the treatment period were similar across all ponesimod groups (73.9–77.2%) and placebo (74.4%).[18]

Phase III Trial-Kappos et al.[19]

The phase III clinical trial oral Ponesimod (Ponvory®) vs Teriflunomide (Aubagio®) in Relapsing Multiple Sclerosis (OPTIMUM) was a multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study.[19] This two-year study compared the efficacy of ponesimod to teriflunomide (a pyrimidine synthesis inhibitor) for the treatment of R-MS based on relapse rate, fatigue, MRI disease activity, tissue loss, and disability accumulation. A total of 1133 participants aged 18-55 years that had been diagnosed with R-MS per the revised (2010) McDonald criteria, EDSS scores of 0 to 5.5, and recent clinical or MRI of disease activity were included in the study. The primary outcome measured was the annualized relapse rate (ARR). Secondary outcomes included changes from baseline in fatigue related symptoms measured by the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) at week 108, cumulative number of combined unique active lesions (CUALs) per year from baseline to end of treatment (EOT), and time to 12- week and 24-week confirmed disability accumulation (CDA) from baseline to EOT. Exploratory endpoints were included to measure the percentage change in brain volume and no evidence of disease activity (NEDA-3 and NEDA-4) status. Safety was assessed using predefined adverse events of special interest (AESIs).[19]

All participants were randomized (1:1) to ponesimod 20 mg orally daily or teriflunomide 14 mg orally daily for the 108-week double-blind treatment period.[19] In the full analysis 567 participants were randomized to the ponesimod group and 566 to the teriflunomide group. Visits were conducted at weeks 2, 4, and 12 weeks after randomization with subsequent visits every 12 weeks thereafter. Safety follow up visits were approximately 14-30 days after the last study dose to mitigate the first-dose cardiac effects participants received a 14-day gradual up-titration (or mockup-titration) of ponesimod starting at 2 mg on Day 1 to 10 mg on Day 14 followed by the 20 mg maintenance dose on Day 15 to

Table 2 | Primary and Secondary Outcomes from Ponesimod Phase II and III Trials[18,19]

Trial	Treatment Duration	Outcomes	Intervention	Result (95% CI)	P-Value
NCT01006265 (n=464) Phase IIb	24 weeks	Cumulative number of new T1 Gd+ lesions at 12-24 weeks	Placebo	6.2	—
			Ponesimod 10 mg	3.5 (0.34-0.95)[a]	0.0318
			Ponesimod 20 mg	1.1 (0.1-0.29)[a]	<0.0001
			Ponesimod 40 mg	1.4 (0.13-0.38)[a]	<0.0001
		ARR[b]	Placebo	0.525 (0.358-0.77)	—
			Ponesimod 10 mg	0.332 (0.198-0.557)	0.1619
			Ponesimod 20 mg	0.417 (0.226-0.653)	0.4420
			Ponesimod 40 mg	0.251 (0.141-0.446)	0.0363
		Time to first confirmed relapse at 24 weeks	Placebo	78.5 (70.98-85.96)	—
			Ponesimod 10 mg	85.6 (78.59-92.6)	0.1744
			Ponesimod 20 mg	83.9 (76.9-90.96)	0.4529
			Ponesimod 40 mg	90.6 (84.97-96.16)	0.0189
OPTIMUM (n=1133) Phase III	108 weeks	ARR	Ponesimod 20 mg	0.202 (0.173-0.235)	<0.001
			Teriflunomide 14 mg	0.290 (0.254-0.331)	—
		FSIQ-RMS[c]	Ponesimod 20 mg	-0.01	0.002
			Teriflunomide 14 mg	-3.57	—
		CUALs[d]	Ponesimod 20 mg	1.405	<0.001
			Teriflunomide 14 mg	3.164	—
		CDA[e] (12 week)	Ponesimod 20 mg	10.1	0.29
			Teriflunomide 14 mg	12.1	—

[a]Standard error, [b]Annualized relapse rate, [c]Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis, [d]Combined unique active lesions, [e]Confirmed disability accumulation

EOT. The study enrolled a representative R-MS population with a median age of 37 years and 735 women. Baseline characteristics were comparable, with a small imbalance in the presence of enhancing lesions in the teriflunomide group (ponesimod 39.9% vs teriflunomide 45.4%). In both groups, 35% of participants had highly active disease, defined by the number of lapses, MRI activity at baseline, EDSS score, and previous DMT. The ponesimod group had fewer treatment discontinuations due to efficacy compared to the teriflunomide group, but more discontinuations attributable to adverse events and tolerability.[19]

Primary efficacy results showed that ponesimod had a statistically significant lower annualized relapse rate (ARR) of 20.2% compared with teriflunomide 29% (RR 0.695, 99% confidence limit (CL) 0.536-0.902; p < .001).19 The change in FSIQ-RMS weekly symptom score from baseline to week 108 also improved for fatigue symptoms in the ponesimod group vs teriflunomide with a least-square means of 0.01 vs 3.56 (mean difference −3.57, 95% CL −5.83 to −1.32; p = 0.002). Ponesimod reduced the mean number of CUALs per year from baseline to week 108 by 56% compared with teriflunomide (1.405 vs 3.164; RR 0.444, 95% CL 0.364-0.542; p < .001). At week 12 there was no significant difference in the risk of CDA between the two groups, 10.1% vs 12.4% for ponesimod and teriflunomide, respectively (HR 0.83, 95% CL 0.58-1.18; p = 0.29).[19]

Exploratory Outcomes

Brain volume loss at week 108 was lower in ponesimod vs teriflunomide (–0.91% vs –1.25%; p < .001).[19] NEDA-3 status is a composite of no relapse, no 12-week CDA, no Gd+ T1 or new or enlarging T2 lesions and NEDA-4 status is a composite of NEDA-3 plus no brain volume decrease of ≥0.4% from baseline to EOT. The estimated percentage reaching NEDA-3 in the ponesimod group vs teriflunomide was 25.0% vs 16.4% (odds ratio 1.70, 95% CL 1.27-2.28; p< 0.001), respectively. The estimated percentage reaching NEDA-4 was 11.4% vs 6.5% (odds ratio 1.85, 95% CL 1.24-2.76; p = 0.003) in the ponesimod vs teriflunomide groups. Overall, the incidence of treatment-emergent adverse events (TEAE) was 88.8% vs 88.2% and serious treatment-emergent serious adverse events of 8.7% vs 8.1% was similar for ponesimod and teriflunomide, respectively.[19]

Adverse Effects and Precautions

Peripheral lymphocyte counts in the blood are reduced dose-dependently by ponesimod and therefore may increase the susceptibility to infections.[14,15,16] Before initiating treatment, results from a complete blood count with lymphocytes count should be taken within 6 months or after discontinuation of other MS therapy. Initiation should be delayed in patients with active infection until resolution.[16]

Viral herpes infections such as herpes simplex encephalitis and varicella zoster meningitis have been reported with S1P receptor modulators, with a 4.8% incidence for herpetic infections as reported in the OPTIMUM trial for both the ponesimod and teriflunomide groups.[19] Other S1P receptor modulators have been associated with cryptococcal meningitis and disseminated cryptococcal infections leading to fatality.[16] Progressive Multifocal Leukoencephalopathy (PML) has been reported in patients treated with fingolimod, a S1P receptor modulator, and other MS therapies.[16] If PML is suspected, treatment with ponesimod should be held until PML has been resolved. If PML is confirmed, ponesimod should be discontinued.[16]

Table 3 | Common Dose Dependent Ponesimod Adverse Effects[18,19]

Adverse Effect	Incidence Rate
Headache	11.5-13.9%
Nasopharyngitis	9.6-19.3%
ALT[a] Elevation	4.6-19.5%
Shortness of Breath	4.6-14.3%
Upper Respiratory Tract Infection	3.7-10.6%
Peripheral Oedema	1.9-10.9%

In phase II, treatment-emergent adverse events (TEAEs) that had a higher incidence in the three ponesimod groups compared with placebo, as shown in **Table 3**, were anxiety, dizziness, dyspnea, increased alanine aminotransferase, influenza, insomnia, and peripheral oedema.[18] Incidences of dyspnea and peripheral oedema appeared to be dose-related, with substantially more cases reported in the ponesimod 40 mg group compared with the ponesimod 10 and 20 mg groups. Cardiac AEs associated with ponesimod initiation was first degree heart block (1.2%), second-degree atrioventricular block (0.9%), and bradycardia (2%). All cardiac AEs related to heart rhythm occurred on Day 1 and had no recurrence later during treatment. On up-titration days (Days 8 and 15), heart rate changes with the higher doses of ponesimod were small and similar in the placebo group.[18]

In phase III, common TEAEs (≥10%) were increased alanine aminotransferase (ALT) levels nasopharyngitis, headache, upper respiratory tract infection, and alopecia in the ponesimod vs teriflunomide groups, respectively as seen in **Table 3**.[19] Most frequently occurring adverse events of special interest (AESIs; occurring up to the EOT plus 15 days, unless otherwise specified) with ponesimod vs teriflunomide were in the categories of hepatobiliary disorders or liver enzyme abnormalities (up to EOT plus 1 day) (22.7% vs 12.2%), hypertension, pulmonary events (8.0% vs 2.7%), and herpetic infection. The most frequently reported pulmonary AESI was dyspnea. Treatment discontinuations due to adverse events was more common in the ponesimod group (8.7% vs 6.0%) for dyspnea, increased liver enzymes, and macular edema. Incidence of first-dose heart rate and rhythm AESIs on Day 1 of treatment up-titration with 2 mg of ponesimod was 2.1% in the ponesimod group and 0.4% in the teriflunomide group. No second degree or higher AV blocks occurred. The maximum mean reduction in heart rate observed at pre-dose to two hours post-dose in the ponesimod group was −8.7 compared with −1.7 in the teriflunomide group.[19] A summary of the adverse event data from the phase II and III clinical trials can be found on **Table 3**.

Dosage and Administration

Prior to initiation of treatment, a complete blood count from the last six months, electrocardiogram to determine if any preexisting conduction abnormalities exist, liver function test of transaminase and bilirubin within the last six months, ophthalmic evaluation, current list of medications that have immune system effects, and vaccinations need to be evaluated.[16]

The first dose should be administered in a setting where resources to manage symptomatic bradycardia are available. Four-hour monitoring is recommended for patients with sinus bradycardia, first- or second-degree AV block, or a history of myocardial infarction or heart failure more than six months prior to ponesimod initiation and in stable condition. Ponesimod is initiated with

a 14-day titration, starting with one 2 mg tablet by mouth once daily and progressing with the titration schedule. After the dose titration is complete the patient will start the recommended maintenance dose of 20 mg by mouth daily on Day 15. Ponesimod should be swallowed whole and can be taken with or without food.[16]

Special populations

Renal impairment

A study comparing the C_{max} and AUC of ponesimod in adult subjects with moderate to severe renal impairment (creatine clearance between 30-59 ml/min) and healthy individuals (creatinine clearance >90 ml/min) found no significant differences in maximum serum concentrations or exposure.[16,20] There is no data on the effect of dialysis on the pharmacokinetics of ponesimod, however ponesimod is highly bound to plasma protein. Therefore, dialysis is not expected to effect plasma concentrations. No dose adjustments are needed in patients with renal impairment based on these results.[16,20]

Hepatic impairment

In adult subjects with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively) the AUC and $T_{1/2}$ of ponesimod increased based on severity of hepatic impairment compared to healthy individuals.[17] Therefore, ponesimod is not recommended in moderate or severe impairment.[16,20]

Pregnancy & Lactation

Women of childbearing potential should use contraception before initiating treatment with ponesimod and for one week after discontinuation.[16] There are no studies in pregnant females at this time. In animal models administration during pregnancy resulted in increased incidences of fetal malformations, embryo fetal death and post-implantation loss were noted at high doses ponesimod. There are no trials evaluating the presence of ponesimod in human milk, the risks of exposure to a breastfed infant, or the drug's effects on milk production. An animal study showed that ponesimod, when administered orally to female rats during pregnancy and lactation, was detected in the serum plasma of the offspring. The health and developmental benefits of breastfeeding should be weighed with the mothers need for ponesimod and any potential adverse effects to the infant from breastfeeding.[16]

Drug Interactions

Ponesimod has not been studied concomitantly with antineoplastic, immune-modulating, or immunosuppressive drugs.[16] Combining ponesimod or switching drugs with these therapies increases the risk of additive immune effects. Alemtuzumab should not be initiated with ponesimod because of the characteristics and duration of alemtuzumab's immune suppressive effects.[17] Concomitant use of strong CYP3A4 and UGT1A1 inducers may decrease the systemic exposure of ponesimod as indicated from in vitro assessments. It is unclear if the reduction in ponesimod concentrations would be clinically relevant but coadministrations of ponesimod with strong CYP3A4 and UGT1A1 inducers is not recommended. During and up to 1-2 weeks after discontinuation of treatment with ponesimod vaccinations may be less effective. Live attenuated vaccines may carry the risk of infection and should be avoided during ponesimod treatment and for up to 1-2 weeks after discontinuation.[16]

Caution should be used when initiating treatment of ponesimod in patients on a beta-blocker because of the additive effects on lowering the heart rate, however, patients on stable doses of ponesimod can be initiated on beta-blocker treatment. Ponesimod has not been studied in patients taking QTc prolonging agents with known risks of torsade de pointes and should not be initiated because of the effects on heart rate.[16] If receiving concomitant therapy with heart rate slowing drugs a cardiologist should be consulted before considering initiating treatment with ponesimod.[16]

Cost

The wholesale acquisition cost (WAC) of ponesimod per month is $8,083.50, which translates to about $97,002 per year.[21] The WAC is similar to the listed out-of-pocket cost without insurance. At the time of this article ponesimod is a new to market drug, therefore insurance plans may be awaiting review from their pharmacy and therapeutic committee before placing it on a formulary tier. Per the manufacturer, cost savings are available through commercial rebates and patient assistance savings card to those who qualify.[22]

Clinical Implications

Ponvory® (ponesimod) is the fourth and most recently approved sphingosine 1-phosphate receptor modulator on the market. Other medications in this class include ozanimod (approved 2020), siponimod (approved 2019), and the first in class fingolimod (approved 2010).

Generally, first line agents for relapsing MS are the interferon beta 1a, 1b and glatiramer acetate injectables. Fingolimod is a highly favored oral S1P receptor modulator for MS, however the newer second-generation agents have gained more popularity by physicians.[23] Among the S1P receptor modulators ponesimod is the most selective for S1P1.

Ponesimod does not have a definitive place in therapy for the treatment of relapsing MS. The American Academy of Neurology (AAN) 2018 guidelines provide broad and general recommendations but lack a reliable treatment algorithm. There is a lack of data on well-controlled head-to-head comparisons, differences in efficacy, tolerability, route of administration, and safety. Selection greatly depends on patient and provider preference through shared decision making. Highly effective DMTs provide better long-term outcomes if prescribed early in treatment. Ponesimod, appears to be a highly effective S1P receptor modulator, therefore could be used earlier in the disease course when indicated. A systematic review and network meta-analysis (NMA) comparing the efficacy and acceptability of S1P receptors for treating MS patients found that ponesimod 40 mg was the second most beneficial intervention, but the worst accepted based on adverse events leading to discontinuation of a study.[24] Ultimately, the tradeoff between efficacy and tolerability with ponesimod is where the patient's individual preferences and values would be considered.

There are some clear advantages of ponesimod over therapies in the same class. First, ponesimod has a half-life of approximately 33 hours compared to fingolimod that has terminal half-life of approximately eight days (**Table 4**).[15] Ponesimod's short half-life allows faster elimination from the body and ability to reach steady state concentrations. Additionally, ponesimod has a rapid, dose-dependent recovery to baseline lymphocyte counts after discontinuation showing that its pharmacological effects are more rapidly reversible. If ponesimod is discontinued due to vaccination, pregnancy, or switching DMTs it leaves the body within

Table 4 | Comparison of S1P Receptor Modulators[25,30]

S1P Characteristic	Fingolimod	Siponimod	Ozanimod	Ponesimod
Receptor Target	1,3,4,5	1,5	1,5	1,5
Half Life	6-9 days	22-38 hours	19-22 hours	33 hours
Max Reduction in Lymphocyte Counts (%)	73%	70%	68%	70%
Time to Recovery of Baseline Lymphocytes	4-8 weeks	7-10 days	30 days-3 months	7 days
ARR[a]	0.35	0.30	0.24	0.25
Amount of Gd+ T1 lesions	1.29 ± 5.8 at 6 months[c]	0.28 at 6 months[d]	1.5 at 12-24 weeks[e]	1.4 at 12-24 weeks[f]
Mean combined unique active lesions	—	0.36 at 3 months[d]	—	1.9 at 12-24 weeks[f]
Bradycardia	3% at 5mg dose[c]	28%[d]	0.6% at 0.25mg dose[e]	2% at 10mg dose[f]
Increase in ALT[b] (>3 times normal limit)	10%[c]	4%[d]	1.2%[e]	4.2%[f]
FDA[c] Approved Indications		Relapsing Remitting Multiple Sclerosis (RR-MS) Secondary Progressive Multiple Sclerosis (SP-MS) Clinically Isolated Syndrome		

[a]Annualized relapse rate; [b]alanine aminotransferase; [c]1.25mg Kappos, et al. Phase II, 6 months; [d]10mg BOLD Phase II, 6 months; [e]1mg RADIANCE Phase II, 6 months; [f]40mg Olsson, et al. Phase II, 6 months

one week. Regarding pregnancy, contraception with ponesimod needs to be continued for only up to seven days after treatment discontinuation, compared to three months with ozanimod, ten days with siponimod, and two months with fingolimod. These differences allow flexibility in retreatment with other agents, aid in the washout period to treat potential opportunistic infections and address other treatment-related complications.[25]

A real-world limitation of ponesimod would be the complex titration schedule needed for the initiation and re-initiation of ponesimod. For four or more consecutively missed doses during titration or maintenance the patient must restart the titration from Day 1.[16] This is not only a burden in terms of adherence but also for cost, because the 14-day starter pack would require a separate prescription from the 20 mg maintenance dose tablets. Another limitation in the real world would be the requirement for monitoring at treatment initiation. Ponesimod, siponimod, and fingolimod all recommend monitoring for signs of bradycardia for at least six hours after the first dose. Ozanimod does not recommend or require first dose monitoring.[16,26,27,28] An alternative agent like ozanimod might be more favorable to physicians because it does not require the six-hour first dose monitoring guideline. Another benefit of ponesimod is that is does not require any genetic testing prior to treatment unlike siponimod which requires CYP2C9 genotype determination. Finally, ponesimod has not been evaluated in pediatrics. In 2018 the FDA approved fingolimod for RMS in children aged 10-18 years old. It is the first and only S1P receptor modulator studied in pediatrics.[29,30]

The phase II and III studies were adequately designed in cohort size, primary outcome, and treatment duration. A limitation in the phase II trial was the exclusion criteria. The investigators did not exclude participants that had significant medical conditions or that were on therapies for cardiovascular, pulmonary, immunological, hepatic, or ophthalmic conditions like in phase III. The only exclusion criteria of clinically relevant medical condition that would put the subject at risk by participating, as determined by the investigator, was reported and too broad. This left the potential for confounders in the adverse effect analysis. Other exclusions from the phase III trial included contraindications to MRI and pregnant/lactating women.

The OPTIMUM trial assessed fatigue using the FSIQ-RMS scale which was specifically developed to assess fatigue in patients with RMS following the FDA's Guidance of Industry on Patient Reported Outcome Measures.[19] No previous phase III study has assessed fatigue as an outcome measure despite the well-known implications on quality of life and high socioeconomic burden.[19] At baseline fatigue symptom scores were comparable between ponesimod and teriflunomide. From baseline to week 108 patients in the ponesimod group had a significant reduction in fatigue symptoms compared to the teriflunomide group. The OPTIMUM trial did a good job at prospectively addressing fatigue as a secondary outcome and demonstrating the added benefit of ponesimod over teriflunomide.

Conclusion

PONVORY® (ponesimod) is a reversible, selective, and orally active sphingosine 1-phosphate receptor 1 modulator that was approved by the FDA in March 2021 for the treatment of relapsing multiple sclerosis in adults.[12,13] There is currently no gold standard treatment option for RMS and providers rely on disease characteristics and shared decision making with the patients when choosing the treatment plan. Additional studies assessing long-term reduction in disease progression and adverse effects are needed. Comparative DMT and head-to-head studies are also needed to better understand the benefits of ponesimod over other therapies and determine if greater selectivity decreases treatment emergent risks and increases biological effectiveness.

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