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PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **PONVORY™**

Ponesimod tablets,

Film-Coated tablets, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg, oral

Sphingosine 1-phosphate receptor modulator

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Date of Initial Approval:
April 28, 2021

Submission Control No: 239537

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PrPONVORY™ (ponesimod) is indicated for:

The treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

PONVORY™ should only be prescribed by neurologists who are experienced in the treatment of multiple sclerosis and are knowledgeable of the efficacy and safety profile of PONVORY™ and are able to discuss benefits/harms with patients.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of PONVORY™ have not been evaluated in pediatric patients. PONVORY™ is not indicated for treatment of patients under 18 years of age.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of PONVORY™ did not include patients aged 65 years and older. Therefore, it is not known whether the safety and efficacy differ in elderly patients compared to younger patients (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

PONVORY™ is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment (e.g., antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation, or bone marrow transplantation) or disease (e.g., immunodeficiency syndrome).

- Patients with severe active infections including active bacterial, fungal or viral infections (e.g., hepatitis, tuberculosis), until resolution of the infection.

- Patients with known active malignancies, except localized basal cell carcinoma of the skin.

- Patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays).

- Patients with presence of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sinoatrial heart block unless the patient has a functioning pacemaker (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

- Patients with moderate or severe hepatic impairment (Child-Pugh Class B and C; see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

- During pregnancy and in women of childbearing potential not using highly effective contraception (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations 7.1.1 Pregnant Women; 7.1.2 Breast-feeding).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For patient monitoring and assessment before initiating treatment with PONVORY™, see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

4.2 Recommended Dose and Dosage Adjustment

PONVORY™ film-coated tablets for oral use are provided in the Initiation Pack of strengths of 2, 3, 4, 5, 6, 7, 8, 9, and 10 mg ponesimod. The Maintenance Pack includes ponesimod 20 mg tablets.

Up-Titration Dose:

The Initiation Pack must be used for patients initiating treatment with PONVORY™ (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

Initiate PONVORY™ treatment with a 14 day up-titration; start with administration of one 2 mg tablet orally once daily and progress with the titration schedule outlined in the Table 1 below (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Up-Titration for reduction in heart rate).

Table 1: Dose Titration Regimen

Titration Day	Daily Dose
Day 1 and Day 2	2 mg once daily
Day 3 and Day 4	3 mg once daily
Day 5 and Day 6	4 mg once daily
Day 7	5 mg once daily
Day 8	6 mg once daily
Day 9	7 mg once daily
Day 10	8 mg once daily
Day 11	9 mg once daily
Day 12, Day 13 and Day 14	10 mg once daily

If dose titration is interrupted, missed dose instructions must be followed (see 4 DOSAGE AND ADMINISTRATION, 4.5 Missed Dose).

Maintenance Dose:

After dose titration is complete, the recommended maintenance dosage of PONVORY™ is one 20 mg tablet taken orally once daily.

Re-initiation of maintenance therapy after treatment interruption

Interruption during treatment, especially during up-titration, should be avoided, however:

- If less than 4 consecutive doses are missed, resume treatment with the first missed dose.
- If 4 or more consecutive doses are missed, reinitiate treatment with Day 1 (2mg) of the up-titration regimen.

If ponesimod therapy is discontinued for 4 or more consecutive days, the effects on heart rate and AV conduction may recur on reintroduction of ponesimod treatment and the same

precautions as for the first dose should apply. During treatment initiation or maintenance, if treatment needs to be reinitiated with Day 1 of the titration regimen, first-dose monitoring must be completed in patients for whom it is recommended (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

Special Populations

Pediatric patients (below 18 years)

The safety and efficacy of PONVORY™ have not been established in pediatric patients aged 18 years and younger. PONVORY™ is not indicated for use in pediatric patients.

Geriatric patients (65 years or above)

Clinical studies of ponesimod did not include patients aged 65 years and older to determine whether they respond differently from younger subjects, therefore PONVORY™ should be used with caution in this population.

Renal Impairment

Based on clinical pharmacology studies, no dose adjustment is needed in patients with mild to severe renal impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Impairment).

Hepatic Impairment

PONVORY™ is contraindicated in adult subjects with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively), as the risk of adverse reactions may be greater (see 2 CONTRAINDICATIONS). No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Impairment).

Based on clinical pharmacology studies in adult subjects with mild, moderate, or severe hepatic impairment, ponesimod $AUC_{0-\infty}$ was increased 1.3, 2.0-and 3.1-fold respectively, compared to healthy subjects (10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Impairment).

Cardiac effects

Initiation of treatment with PONVORY™ causes a transient decrease in heart rate and atrioventricular conduction delays. Prescribers should:

- Obtain an electrocardiogram (ECG) for all patients to determine whether pre-existing conduction abnormalities are present (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular - Assessments Prior to Initiating PONVORY™ to Guide Patient Treatment).

- Determine whether patients are taking concomitant medications that reduce heart rate or atrioventricular conduction (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular - Bradyarrhythmia and Atrioventricular Conduction Delays and 9 DRUG INTERACTIONS).

- For patients with sinus bradycardia (heart rate (HR) <55 bpm), first or second-degree [Mobitz type I] atrioventricular block (AV block), or a history of myocardial infarction or heart failure, prepare to administer the first dose of PONVORY™ in a clinical setting where they can be monitored for signs and symptoms of bradycardia, with hourly pulse and blood pressure measurements for at least 4 hours, and where symptomatic

bradycardia can be managed (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

- For patients with certain other pre-existing cardiac conditions, seek an evaluation from a cardiologist prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

4.4 Administration

PONVORY™ should be administered orally once daily. The tablet should be swallowed whole. PONVORY™ can be taken with or without food.

4.5 Missed Dose

See 4.2 Recommended Dose and Dosage Adjustment for missed dose or interruption during treatment.

5 OVERDOSAGE

In patients with overdosage of PONVORY™, especially upon initiation/re-initiation of treatment, it is important to observe for signs and symptoms of bradycardia as well as atrioventricular (AV) conduction blocks, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; Bradyarrhythmia and Atrioventricular Conduction Delays, Cardiovascular, Increased Blood Pressure; 10.2 Pharmacodynamics, Heart Rate and Rhythm).

There is no specific antidote to ponesimod. Neither dialysis nor plasma exchange would result in meaningful removal of ponesimod from the body. The decrease in heart rate induced by PONVORY™ can be reversed by atropine. In the event of overdose, PONVORY™ should be discontinued, and general supportive treatment given until clinical toxicity has been diminished or resolved. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Initiation Pack: Film-coated tablets containing ponesimod: 2 mg (5.0mm white tablet debossed with "2" on one side and arch on the other side), 3 mg (5.0mm red tablet debossed with "3" on one side and arch on the other side), 4 mg (5.0mm purple tablet debossed with "4" on one side and arch on the other side), 5 mg (8.6mm green tablet debossed with "5" on one side and "A" on the other side), 6 mg (8.6mm white tablet debossed with "6" on one side and "A" on the other side), 7 mg (8.6mm red tablet debossed with "7" on one side and "A" on the other side), 8 mg (8.6mm purple tablet debossed with "8" on one side and "A" on the other side), 9 mg (8.6mm brown tablet debossed with "9" on one side and "A" on the other side) 10 mg (8.6mm orange tablet debossed with "10" on one side and "A" on the other side) Maintenance Pack: 20 mg ponesimod (8.6mm yellow tablet debossed with "20" on one side and "A" on the other side)	Tablet Core: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, silica colloidal anhydrous and sodium laurilsulfate. Tablet Coating (Opadry II): hydroxypropyl methylcellulose, iron oxide red (included in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg and 10 mg film-coated tablets), iron oxide black (included in 4 mg, 5 mg, 8 mg and 9 mg film-coated tablets), iron oxide yellow (included in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg and 20 mg film-coated tablets), lactose monohydrate, polyethylene glycol 3350, titanium dioxide, and triacetin.

PONVORY™ is available as round, biconvex, film-coated tablets for oral use in Initiation packs for the up-titration regimen and Maintenance Packs for maintenance dosage.

PONVORY™ Initiation Pack is supplied in blister packaging containing 14 tablets.
The Maintenance Pack is in blister packaging containing 28 tablets.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of PONVORY™ treatment results in a transient decrease in heart rate and atrioventricular (AV) conduction delays, an up-titration scheme must be used to reach the maintenance dosage of PONVORY™ 20 mg (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Heart Rate and Rhythm).

PONVORY™ was not studied in patients who had:

- Myocardial infarction unstable angina pectoris, stroke/transient ischemic attack or unstable ischemic heart disease in the last 6 months (see 2 CONTRAINDICATIONS)
- Cardiac failure (New York Heart Association class III-IV) or presence of any severe cardiac disease (see 2 CONTRAINDICATIONS)
- Cardiac conduction or rhythm disorders (including complete left bundle branch block, sinus arrest, sinoatrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest) either in history or observed at screening
- Cardiac arrhythmias requiring treatment with Class Ia or III antiarrhythmic drugs
- Mobitz Type II second degree AV block or higher-grade AV block observed at screening (see 2 CONTRAINDICATIONS)
- QTcF interval greater than 470 ms (females), and greater than 450 ms (males) observed at screening
- Resting HR < 50 bpm

Reduction in Heart Rate

After the first dose of PONVORY™, the decrease in heart rate (HR) typically begins within an hour and reaches its nadir within 2-4 hours. The heart rate typically recovers to baseline levels 4-5 hours after administration of the first dose. The mean decrease in heart rate on Day 1 of dosing was 6 bpm. With up-titration after Day 1, the decrease in heart rate is less pronounced.

In the OPTIMUM study, bradycardia at treatment initiation (sinus bradycardia on ECG (HR less than 50 bpm)) occurred in 5.8% of PONVORY™ treated patients compared to 1.6% of patients receiving teriflunomide. Patients who experienced bradycardia were generally asymptomatic. Bradycardia resolved in all patients without intervention and did not require discontinuation of PONVORY™ treatment. On Day 1, 3 patients treated with PONVORY™ had asymptomatic post dose HR below or equal to 40 bpm; all 3 patients had baseline HRs below 55 bpm (see 8 ADVERSE REACTIONS, Bradyarrhythmia; 9 DRUG INTERACTIONS; and 10 CLINICAL PHARMACOLOGY, Heart rate and rhythm).

Atrioventricular Conduction Delays

Initiation of PONVORY™ treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. In the OPTIMUM study, the AV conduction delays manifested as first-degree AV block (prolonged PR interval on ECG), which occurred in 3.4% of PONVORY™ treated patients and in 1.2% of patients receiving teriflunomide. No second-degree AV blocks, Mobitz type I (Wenckebach), were observed in OPTIMUM. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, resolved without intervention,

and did not require discontinuation of PONVORY™ treatment.

QTc Prolongation

In a thorough QT interval study, supratherapeutic doses of 40 and 100 mg tablets in healthy subjects showed that ponesimod was associated with QTc prolongation (see 10 CLINICAL PHARMACOLOGY, Effect on QT/QTc Interval and Cardiac Electrophysiology).

If treatment with PONVORY™ is considered in patients with pre-existing significant QT prolongation, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

Some drugs causing QTc prolongation have led to an increased risk of ventricular arrhythmias including Torsade de Pointes. Caution should be observed if PONVORY™ is administered to patients who have risk factors for Torsade de Pointes including the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; congenital long QT syndromes; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) and bradycardia. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to PONVORY™ administration. Particular care should be exercised when administering PONVORY™ treatment to patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QTc-prolonging drug.

PONVORY™ has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. disopyramide, procainamide) or Class III anti-arrhythmic drugs (e.g. amiodarone, sotalol). Class Ia and Class III anti-arrhythmic drugs have been associated with cases of Torsade de Pointes in patients with bradycardia. PONVORY™ should not be used concomitantly with these drugs during treatment initiation (see 9 DRUG INTERACTIONS).

PONVORY™ has not been studied in patients treated with drugs that prolong the QTc interval. Because the risk of QTc interval prolongation is expected to be greater in patients who receive concomitant treatment with other drugs that prolong the QTc interval, the use of PONVORY™ with such drugs should be avoided. If treatment with PONVORY™ is considered, such patients should be evaluated by a cardiologist prior to initiation of treatment to assess suitability and to determine the most appropriate monitoring, which may include overnight (see 9 DRUG INTERACTIONS).

If treatment with PONVORY™ is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec).
- In patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia or Class III anti-arrhythmic drugs (see 9 DRUG INTERACTIONS, Anti-arrhythmic Drugs, QT Prolonging Drugs, Drugs that may decrease heart rate).
- In patients with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), and uncontrolled hypertension (see 2 CONTRAINDICATIONS).

PONVORY™ should not be used in:

- In patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure (see 2 CONTRAINDICATIONS)
- Patients with presence of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sinoatrial heart block unless the patient has a

functioning pacemaker (see 2 CONTRAINDICATIONS)

Increased Blood Pressure

In the OPTIMUM study, PONVORY™ treated patients had an average increase of 2.9 mmHg in systolic blood pressure and 2.8 mmHg in diastolic blood pressure compared to 2.8 mmHg and 3.1 mmHg in patients receiving teriflunomide, respectively. An increase in blood pressure with PONVORY™ was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. The blood pressure values after PONVORY™ treatment discontinuation indicate reversibility. Hypertension was reported as an adverse reaction in 10% of PONVORY™ -treated patients and in 9.0% of patients receiving teriflunomide. One patient experienced a hypertensive crisis but had evidence of long-standing hypertensive heart disease. Blood pressure should be monitored during treatment with PONVORY™ and managed appropriately.

Dependence/Tolerance

No studies on the abuse liability of PONVORY™ have been performed.

Driving and Operating Machinery

No studies on the effects of PONVORY™ on the ability to drive or use machinery have been performed.

Hepatic/Biliary/Pancreatic

Liver Injury

Elevations of transaminases (AST/ALT) may occur in PONVORY™ -treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of PONVORY™ therapy (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

During treatment with PONVORY™, liver transaminases (ALT/AST) and bilirubin levels should be evaluated within the first 3 months of starting treatment, and periodically or as clinically indicated thereafter. Treatment with PONVORY™ should be interrupted with repeated clinically significant increases of these parameters and should only be re-initiated once levels have normalized. The benefits and risks of treatment should be re-assessed prior to re-initiation of treatment. When re-initiating treatment, consider all relevant assessments and monitoring for treatment initiation (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Treatment Initiation Recommendations).

In the OPTIMUM study, ALT increased to three and five times the upper limit of normal (ULN) in 17.3% and 4.6% of PONVORY™ -treated patients, respectively, compared to 8.3% and 2.5% of patients receiving teriflunomide, respectively. ALT increased eight times ULN in 0.7% PONVORY™ -treated patients compared to 2.1% in patients receiving teriflunomide. The majority of elevations occurred within 6 to 12 months of starting treatment. Most cases of ALT increases ≥3×ULN resolved on continued PONVORY™ treatment, and the remaining cases resolved upon treatment discontinuation. In clinical trials, PONVORY™ was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should be monitored for hepatotoxicity. PONVORY™ should be discontinued if

significant liver injury is confirmed.

Multiple sclerosis patients with significant concomitant liver disease were excluded from clinical trials with PONVORY™. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking PONVORY™, caution should be exercised when using PONVORY™ in patients with a history of significant liver disease. (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Impairment)

Immune

Risk of Infections
PONVORY™ causes a dose-dependent reduction in peripheral lymphocyte count to 30-40% of baseline values due to reversible sequestration of lymphocytes in lymphoid tissues.

PONVORY™ may therefore increase the risk of infections. No cases of fatal infections have been reported in PONVORY™ treated patients in the development program, however, life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators.

In the Phase 3 OPTIMUM study, the overall rate of infections was comparable between the PONVORY™ treated patients and those receiving teriflunomide (54.2% vs 52.1% respectively). Nasopharyngitis and viral infections were more common in PONVORY™ treated patients. (see 8.2 Clinical Trial Adverse Reactions).

Serious or severe infections occurred in 1.6% in PONVORY™ treated patients compared to 0.9% of patients receiving teriflunomide.

Before initiating treatment with PONVORY™, results from a recent complete blood count with differential (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). In addition, during treatment with PONVORY™, the following should be considered:

Periodic assessments of CBC. Absolute lymphocyte counts <0.2 x 10^9/L, if confirmed, should lead to interruption of PONVORY™ therapy until the level reaches >0.8x10^9/L. Re-initiation of PONVORY™ can then be considered.

- Suspension of treatment with PONVORY™ should be considered if a patient develops a serious infection until resolution of the infection. Patients receiving PONVORY™ should be instructed to promptly report symptoms of infections to their physician to facilitate early and effective diagnostic and therapeutic strategies.

Initiation of treatment with PONVORY™ should be delayed in patients with severe active infection until resolution. In the development program, pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, were restored to normal within 1 week after discontinuation of PONVORY™. In the OPTIMUM study, peripheral lymphocyte counts were restored to normal within 2 weeks after discontinuation of PONVORY™, which was the first timepoint evaluated. Vigilance for signs and symptoms of infection should be continued for 1-2 weeks after PONVORY™ is discontinued (see 7 WARNINGS AND PRECAUTIONS, Immune, Reversibility of Immune System Effects After Stopping PONVORY™).

Herpes Viral Infections
Physicians should be vigilant for clinical symptoms that may be suggestive of serious herpetic infections. Cases of herpes viral infection have been reported in the development program of PONVORY™.

In the OPTIMUM study, the proportion of patients with herpetic infections was 4.8% for both PONVORY™ treated patients and those receiving teriflunomide. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, Immune, Vaccinations).

Cryptococcal Infections
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with other S1P receptor modulators. No cases of CM have been reported in PONVORY™ treated patients in the development program. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. PONVORY™ treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in PONVORY™ treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with PONVORY™ should be suspended until PML has been excluded. If PML is confirmed, treatment with PONVORY™ should be discontinued.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-modulating, or Immunosuppressive therapies
Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects (see 9 DRUG INTERACTIONS, Anti-neoplastic, Immune-modulating, or Immunosuppressive Therapies).

Vaccinations
Patients without a healthcare professional confirmed history of chickenpox (varicella) or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating PONVORY™ treatment. A full course of vaccination for antibody negative patients with varicella vaccine is recommended prior to commencing treatment with PONVORY™. Delay treatment with PONVORY™ for 4 weeks after vaccination to

allow the full effect of vaccination to occur.

No clinical data are available on the efficacy and safety of vaccinations in patients taking PONVORY™. Vaccinations maybe less effective if administered during PONVORY™ treatment. The use of live attenuated vaccines should be avoided while patients are taking PONVORY™. If the use of live attenuated vaccine immunization is required, PONVORY™ treatment should be paused from 1 week prior to 4 weeks after a planned vaccination (see 9 DRUG INTERACTIONS Vaccines).

Human papilloma virus (HPV) infections, including papilloma, dysplasia, warts and HPV-related cancer, have been reported under treatment with another S1P receptor modulator in post-marketing experience. Due to the immunosuppressive properties of PONVORY™, vaccination against HPV should be considered prior to treatment initiation with PONVORY™ taking into account vaccination recommendations (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests).

Unintended Additive Immunosuppressive Effects from Prior Treatment with Immunosuppressive or Immune-modulating Therapies
When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive effects on the immune system while at the same time minimizing risk of disease reactivation, when initiating PONVORY™.

Reversibility of Immune System Effects After Stopping PONVORY™
After stopping PONVORY™ therapy, ponesimod remains in the blood for up to 1 week. Pharmacokinetic/pharmacodynamic modeling indicates lymphocyte counts returned to the normal range in >90% of healthy subjects within 1 week of stopping therapy (see 10 CLINICAL PHARMACOLOGY,10.2 Pharmacodynamics, Immune system).

In the ponesimod development program, pharmacodynamic effects, such as lowering of peripheral lymphocyte counts, were restored to normal within 1 week after the last dose.

Use of immunosuppressants may lead to an additive effect on the immune system, and therefore caution should be applied up to 1 week after the last dose of PONVORY™.

Severe exacerbation of disease after stopping PONVORY™
Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping PONVORY™ treatment. Patients should be observed for a severe increase in disability upon PONVORY™ discontinuation and appropriate treatment should be instituted, as required.

Monitoring and Laboratory Tests

Assessments Prior to Initiating* PONVORY™ *to Guide Patient Treatment:

Complete Blood Count
Review results of a complete blood count (CBC) with differential White Blood Cell (WBC) count obtained within the last 6 months (see 7 WARNINGS AND PRECAUTIONS, Immune, Risk of Infections).

Liver Function Tests
PONVORY™ is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B and C). Review results of transaminase (ALT/AST) and bilirubin levels obtained within the last 6 months (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver Injury).

Pregnancy Test
PONVORY™ is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraception. Before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available (see 7.1 Special Populations, 7.1.1 Pregnant Women).

Ophthalmic evaluation
PONVORY™ increases the risk of macular edema. Obtain an evaluation of the fundus, including the macula (see 7 WARNINGS AND PRECAUTIONS, Macular Edema).

Cardiac evaluation
PONVORY™ is contraindicated in patients with presence of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sinoatrial heart block unless the patient has a functioning pacemaker. Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist and first-dose monitoring is recommended (see WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays).

Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction (see 9 DRUG INTERACTIONS, Anti-arrhythmic Drugs, QT Prolonging Drugs, Drugs that may decrease heart rate and Beta-Blockers).

Current or Prior medications
PONVORY™ is contraindicated in patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment, e.g., antineoplastic, immunosuppressive or immunomodulating therapies. If there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, Immune, Risk of Infections; 9 DRUG INTERACTIONS, Anti-neoplastic, Immunosuppressive, or Immune-modulating Therapies).

Vaccinations
Test patients for antibodies to varicella zoster virus (VZV) before initiating PONVORY™; a full course of VZV vaccination for antibody-negative patients is recommended prior to commencing treatment with PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, Immune, Risk of Infections).

Active infection
Delay the initiation of PONVORY™ in patients with severe active infection until resolved (see 2 CONTRAINDICATIONS).

Treatment Initiation Recommendations

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.

- In all patients, a dose titration is recommended for initiation of PONVORY™ treatment to mitigate cardiac effects (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

- In patients with sinus bradycardia, first-or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset more than 6 months prior to initiation, ECG testing and first-dose monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

PONVORY™ is not recommended in patients with a history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), uncontrolled hypertension or untreated sleep apnea, since significant bradycardia may be poorly tolerated in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

- Use of PONVORY™ in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

- Experience with PONVORY™ is limited in patients receiving concurrent therapy with drugs that decrease heart-rate (e.g., beta-blockers, non-dihydropyridine calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate such as digoxin). Concomitant use of these drugs during PONVORY™ initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with PONVORY™ should generally not be initiated in patients who are concurrently treated with these substances. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment to assess suitability of treatment and to determine the most appropriate monitoring:

    - Bradyarrhythmic effects are more pronounced when PONVORY™ is added to beta-blocker therapy (see 9 DRUG INTERACTIONS, Pharmacodynamic Interactions). For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing PONVORY™ treatment. If the resting heart rate is >55 bpm under chronic beta-blocker treatment, PONVORY™ can be introduced. If resting heart rate ≤ 55 bpm, initiation of treatment with PONVORY™ is not recommended. Depending on the benefit-risk, the beta-blocker may be interrupted until the baseline heartrate is >55 bpm. Treatment with PONVORY™ can then be initiated and treatment with a beta-blocker can be reinitiated after PONVORY™ has been up-titrated to the target maintenance dosage (see 9 DRUG INTERACTIONS, Beta-Blockers). If treatment with PONVORY™ is considered in patients who are under chronic beta-blocker treatment, they should be monitored during treatment initiation according to procedures similar to those recommended below for patients with pre-existing cardiac conditions (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

- For patients taking other drugs that decrease heart rate, treatment with PONVORY™ should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions; 9 DRUG INTERACTIONS, Anti-arrhythmic Drugs, QT Prolonging Drugs, Drugs that may decrease heart rate).

First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions

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 less than 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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics).

First-dose 4-hour Monitoring

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 at the end of the 4-hour observation period.

Additional Monitoring after 4-hour-monitoring

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 is less than 45 bpm
- The heart rate is at the lowest value post-dose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 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 pharmacological treatment is required. If pharmacological 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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays).
- 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 Torsades de Pointes (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays; DRUG

INTERACTIONS, Anti-arrhythmic Drugs, QT Prolonging Drugs, Drugs that may decrease heart rate).

- Receiving concurrent therapy with drugs that slow heart rate or AV conduction (see 9 DRUG INTERACTIONS, Anti-arrhythmic Drugs, QT Prolonging Drugs, Drugs that may decrease heart rate, Beta-Blockers).

Materials to assist healthcare professionals with patient management are available through Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781

Neoplasms

One case of malignant melanoma and two cases of basal cell carcinoma were reported in PONVORY™ treated patients. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator. Physicians and patients should remain alert for the potential development of skin malignancies. Periodic cancer screenings are recommended as per standard of care. Patients should be informed against exposure to sunlight without protection and avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Neurologic

Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1 phosphate (S1P) receptor modulator. Such events have not been reported for PONVORY™ treated patients in the development program. However, should a PONVORY™ treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider a MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, PONVORY™ should be discontinued.

Seizures

Caution should be exercised when administering PONVORY™ to patients with pre-existing seizure disorder. In the phase 3 clinical trial, seizures were reported in 1.4% of PONVORY™ patients, compared to 0.2% in patients receiving teriflunomide. It is not known whether these events were related to the effects of Multiple Sclerosis alone, to PONVORY™ or to a combination of both.

Ophthalmologic

Macular Edema

PONVORY™ increases the risk of macular edema. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and again at any time if a patient reports any change in vision while on PONVORY™ therapy (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Assessments Prior to Initiating PONVORY™ to Guide Patient Treatment).

In the clinical trial experience in patients with all doses of ponesimod, the rate of macular edema

was 0.7%. Most cases occurred within the first 6 months of therapy.

In the OPTIMUM study, macular edema was reported in 1.1% of PONVORY™ treated patients compared to none of the patients receiving teriflunomide.

Continuation of PONVORY™ therapy in patients with macular edema has not been evaluated. A decision on whether PONVORY™ should be discontinued must take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of retinal diseases, uveitis and patients with diabetes mellitus are at increased risk of macular edema during therapy with S1P receptor modulators. Therefore, these patients should have regular follow up examinations of the fundus, including the macula, during treatment with PONVORY™.

Psychiatric

Depression and Suicide
Depression and suicidal ideation are known to occur at an increased frequency in MS patients. A relationship between the occurrence of depression and/or suicidal ideation and the use of PONVORY™ has not been established. However, patients treated with PONVORY™ should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physicians.

Reproductive Health: Female and Male Potential

Fetal risk
Based on animal studies, PONVORY™ may cause fetal harm. Because it takes approximately 1 week to eliminate PONVORY™ from the body, women of childbearing potential should use highly effective contraception to avoid pregnancy during and for 1 week after stopping PONVORY™ treatment. (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, 7.1.2 Breast-feeding).

Fertility
Females
PONVORY™ is contraindicated in women of childbearing potential not using highly effective contraception (see 2 CONTRAINDICATIONS).

Before initiation of PONVORY™ treatment in women of childbearing potential, a negative pregnancy test result must be available, and women should be counseled on the potential for a serious risk to the fetus and the need for highly effective contraception during treatment with PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women, 7.1.2 Breast-feeding).

Since it takes approximately 1 week to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women must use highly effective contraception during this period (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health, Fetal Risk).

Males
Animal studies suggest that PONVORY™ does not affect male fertility (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

In the OPTIMUM study, the reduction from baseline in percent predicted Forced Expiratory Volume in 1 second (FEV1) at 2 years was 8.3% in PONVORY™ treated patients compared to 4.4% in patients receiving teriflunomide. Ponesimod effect on the Forced Vital Capacity (FVC) was less pronounced compared to its effect on FEV1. The reduction from baseline in mean percent predicted FVC at Week 108 was 2.8% in the PONVORY™ group compared to 2.9% in the teriflunomide group. The changes in FEV1 and FVC appear to be partially reversible after treatment discontinuation, but there is insufficient information to determine a complete reversibility.

In the OPTIMUM study, 7(1.2%) patients discontinued PONVORY™ because of pulmonary adverse events (dyspnea). No patients discontinued teriflunomide because of pulmonary adverse events. The overall incidence of pulmonary adverse events was rare and similar in both groups, except for dyspnea, which was the leading cause for treatment discontinuation in the PONVORY™ group. Dyspnea was reported in 5.3% (n=30) of PONVORY™ patients versus 1.2% (n=7) of patients in the teriflunomide group.

PONVORY™ has been tested in MS patients with mild to moderate asthma or chronic obstructive pulmonary disease. The changes in FEV1 were similar in this subgroup compared with the subgroup of patients without baseline lung disorders.

PONVORY™ should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (including untreated sleep apnea). Spirometric evaluation of respiratory function should be performed during therapy with PONVORY™ if clinically indicated.

7.1 Special Populations

7.1.1 Pregnant Women

Based on animal studies, PONVORY™ may cause fetal harm. PONVORY™ is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). If a woman becomes pregnant during treatment, PONVORY™ must be immediately discontinued.

Based on human experience in patients receiving another sphingosine 1-phosphate (S1P) receptor modulator, post-marketing data suggest that its use is associated with an increased risk of major congenital malformations.

There are no adequate and well-controlled studies of PONVORY™ in pregnant women.

Based on animal data and its mechanism of action, PONVORY™ can cause embryofetal harm when administered to a pregnant woman (see 16 NON-CLINICAL TOXICOLOGY, Reproductive Toxicology).

Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod-induced developmental toxicity, including embryo lethality and an increase in fetal malformations (skeletal and visceral).

The AUC_{0-24} in rats and rabbits at the no-observed-adverse-effect level (NOAEL) (1 mg/kg/day in both species) are lower than the human systemic exposures at the recommended human dose (RHD) of 20 mg/day.

Clinical studies with ponesimod excluded pregnant women and breastfeeding women. Across all clinical studies 29 pregnancies were reported including 19 ponesimod-treated female subjects. All pregnancy cases were assessed as not related to the study treatment and resulted in protocol-mandated discontinuation of study treatment.

PONVORY Pregnancy Outcomes Enhanced Monitoring (POEM):

Women exposed to PONVORY™ during pregnancy are encouraged to join the PONVORY Pregnancy Outcomes Enhanced Monitoring (POEM) that monitors outcomes of pregnancy. Healthcare professionals will enroll patients by reporting patient pregnancies to the manufacturer Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

Materials to assist healthcare professionals with patient management are available through Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781

7.1.2 Breast-feeding

There are no data on the presence of PONVORY™ in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

A study in lactating rats has shown excretion of ponesimod in milk.

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to abstain from PONVORY™ therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

The safety and efficacy of PONVORY™ has not been evaluated in pediatric patients. PONVORY™ is not indicated for treatment of patients under 18 years of age.

7.1.4 Geriatrics

Clinical studies of ponesimod did not include patients aged 65 and over to determine whether they respond differently from younger subjects, therefore PONVORY™ should be used with caution in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 1438 MS patients have received PONVORY™ at doses of at least 2 mg daily. These patients were included in the OPTIMUM study, a Phase 3, active-controlled study of ponesimod versus teriflunomide, in a Phase 2 placebo controlled study and their uncontrolled extension studies in patients with MS (see 14 CLINICAL TRIALS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In OPTIMUM, 82% of PONVORY™ -treated patients completed 2 years of study treatment, 12% stayed in study beyond safety follow-up. Median treatment duration was 108 weeks (25 months) with PONVORY™ and teriflunomide. The most common adverse reactions in PONVORY™ treated patients were alanine aminotransferase (ALT) increased, nasopharyngitis, and upper respiratory tract infection (Table 3).

Table 3: Treatment-emergent Adverse Events in the Phase 3 OPTIMUM Study (occurring in at least 2% of PONVORY™ -Treated Patients and reported at ≥1% higher rate than in Teriflunomide-Treated Patients*)

System Organ Class Preferred Term	**PONVORY™ (ponesimod) N=565 (%)**	**Teriflunomide N=566 (%)**
Infections and infestations		
Nasopharyngitis	109 (19)	95 (17)
Upper respiratory tract infection	60 (11)	59 (10)
Urinary tract infection	32 (6)	29 (5)
Bronchitis	26 (5)	25 (4)
Influenza	24 (4)	23 (4)
Respiratory tract infection viral	18 (3)	10 (2)
Respiratory tract infection	17 (3)	16 (3)
Pharyngitis	14 (2)	14 (2)
Metabolism and nutrition disorders		
Hypercholesterolemia	13 (2)	3 (1)
Psychiatric disorders		
Anxiety	18 (3)	16 (3)
Nervous system disorders		
Dizziness	28 (5)	15 (3)
Somnolence	18 (3)	9 (2)
Hypoesthesia	14 (2)	14 (2)
Ear and labyrinth disorders		
Vertigo	13 (2)	7 (1)
Vascular disorders		
Hypertension	45 (8)	44 (8)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	30 (5)	7 (1)
Cough	20 (4)	14 (2)
Musculoskeletal and connective tissue disorders		
Pain in extremity	20 (4)	17 (3)
Arthralgia	17 (3)	16 (3)
General disorders and administration site conditions		
Pyrexia	12 (2)	7 (1)
Investigations		
Alanine aminotransferase (ALT) increased	110 (19)	53 (9)
Aspartate aminotransferase (AST) increased	36 (6)	20 (4)
C-reactive protein increased	12 (2)	7 (1)
Hepatic enzyme increased	13 (2)	8 (1)

*Rounded percentages are presented in the table

The most common adverse reactions (incidence at least 5%) in PONVORY™ treated patients in the Phase 2 placebo-controlled study were fatigue, dyspnea, dizziness, and alanine aminotransferase increased. The following additional adverse reactions occurred in at least 2% of PONVORY™ 20 mg-treated patients and at a higher rate than in patients receiving placebo

(but did not meet the ADR reporting rate criteria for inclusion in the OPTIMUM study): rhinitis, fatigue, chest discomfort, edema peripheral, joint swelling, blood cholesterol increased, migraine, insomnia, depression, dyspepsia, dry mouth, bradycardia, back pain, and sinusitis.

Additionally, in the uncontrolled extension trials the adverse reaction of pneumonia was reported.

Description of selected treatment emergent adverse events

During the OPTIMUM study, treatment-emergent (up to 108-week treatment period + 15 days post end of treatment) adverse events (TEAEs) of heart rate and rhythm were observed in 5.1% of subjects in the ponesimod 20 mg group versus 4.2% in the teriflunomide 14 mg group. The Relative Risk of heart rate and rhythm TEAEs relative to teriflunomide was 1.21 (95% CI: 0.714, 2.053) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Bradyarrhythmia

In the OPTIMUM Study, at treatment initiation, sinus bradycardia on ECG (HR <50 bpm) was observed in 5.8% of subjects in the ponesimod 20 mg group versus 1.6% in the teriflunomide 14 mg group; first degree AV block was observed in 3.4% of subjects in the ponesimod 20 mg group versus 1.2% in the teriflunomide 14 mg group. On Day 1, in the subset of ponesimod 20 mg-treated subjects at risk for symptomatic bradyarrhythmia at baseline, the proportion of subjects with a new ECG finding of sinus bradycardia (HR <50 bpm) was 20.0%, compared to 3.0% (all asymptomatic) in the subset of subjects not at risk for symptomatic bradyarrhythmia.

Three subjects at risk for symptomatic bradyarrhythmia in the ponesimod 20 mg group (with HR <55 bpm prior to ponesimod treatment initiation) experienced asymptomatic post-first-dose HR ≤40 bpm compared to none in the subset of subjects not at risk for symptomatic bradyarrhythmia (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Blood pressure
Chronic treatment is associated with an *increase* in blood pressure.

PONVORY™ treated patients had an average increase of 2.9 mmHg in systolic blood pressure and 2.8 mmHg in diastolic blood pressure compared to 2.8 mmHg and 3.1 mmHg in patients receiving teriflunomide, respectively. An increase in blood pressure with PONVORY™ was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Treatment-emergent increases of ≥20 mmHg from baseline in SBP were reported for 24.6% of subjects in the ponesimod 20 mg group and 29.2% in the teriflunomide 14 mg group.

Treatment-emergent increases of ≥15 mmHg from baseline in DBP were reported for 26.2% of subjects in the ponesimod 20 mg group compared to 27.9% in the teriflunomide 14 mg group (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring in less than 2% of PONVORY™ -treated patients and at least 1% higher frequency than in teriflunomide-treated patients were viral infection, herpes zoster, hyperkalemia, laryngitis, lymphocyte count decreased, lymphopenia, macular oedema, transaminases increased, and ligament sprain.

Seizures were reported in 1.4% of PONVORY™ treated patients, compared to 0.2% in patients receiving teriflunomide. It is not known whether these events were related to the effects of MS, to PONVORY™, or to a combination of both (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Dose dependent reductions in forced expiratory volume over 1 second (FEV1) were observed in

patients treated with PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

One case of malignant melanoma and two cases of basal cell carcinoma (0.4%) were reported in PONVORY™ -treated patients compared to one case of basal cell carcinoma (0.2%) in patients receiving teriflunomide. An increased risk of cutaneous malignancies has been reported in association with another S1P modulator (see 7 WARNINGS AND PRECAUTIONS, Neoplasms).

Adverse events led to discontinuation of treatment in 8.7% of PONVORY™ treated patients, compared to 6.0% of teriflunomide treated patients, most commonly due to dyspnea, increased ALT and macular edema.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Liver function tests
Treatment with S1P receptor modulators is associated with an increase in blood levels of transaminases, mostly alanine aminotransferases (ALT). Majority of ALT elevations occurred within 6 or 12 months of initiating PONVORY™ treatment. Most cases of ALT increase ≥3XULN were single transient asymptomatic episodes which resolved either on continued PONVORY™ treatment or upon treatment discontinuation.

In the OPTIMUM study, liver enzyme abnormalities were reported more frequently in patients treated with PONVORY™ (22.7%) as compared to teriflunomide (12.2%), mainly due to increased ALT(17% versus 8%), Increased AST (5.5% versus 3.2 %), Increased hepatic enzyme (2.1% versus 1.4%) and Increased transaminases (1.6% versus 0.5%).

Triglycerides and Cholesterol
In the OPTIMUM study, mean changes from baseline in triglycerides ranged from 0.145 to 0.262 for patients treated with PONVORY™ compared to -0.127 to 0.015 mmol/L for patients treated with teriflunomide.

Treatment emergent increases in cholesterol from baseline to >7.75mmol/L were reported by 8% of patients treated with PONVORY™ compared to 3.5% treated with teriflunomide.

Lymphocyte counts
In OPTIMUM study, the mean percent decrease from baseline in lymphocyte count at last on-treatment timepoint was -61.17% in the ponesimod 20 mg group, compared to -12.49% in the teriflunomide group. The decrease in lymphocyte count was reversible.

Potassium

In the OPTIMUM study potassium levels above 5.5 mmol/L were observed in 57 (10.1%) and 50 (8.8%) of patients and above 6.0 mmol/L in 9 (1.6%) and 18 (3.2%) patients treated with PONVORY™ and teriflunomide, respectively.

Table 4: Laboratory Abnormalities in PONVORY™ -treated patients and Occurring at a Higher Incidence than Teriflunomide (Between Arm Difference >5%)

Laboratory abnormality	PONVORY™ N=565 %	Teriflunomide N=566 %
Alanine aminotransferase ≥3 ULN (U/L)	20%	11%

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The metabolic profile of ponesimod includes multiple independent pathways, involving CYP enzymes (2J2, 3A4, 3A5, 4F3A and 4F12), and non-CYP enzymes, to form two main circulating metabolites, M12 and M13. PONVORY™ also undergoes direct glucuronidation (mainly via UGT1A1 and UGT2B7, but also to a lesser extent via UGT1A3, UGT1A4 and UGT2B4), in addition to other minor direct metabolic pathways.

9.4 Drug-Drug Interactions

Effect of Other Drugs on Ponesimod

Drugs that are inhibitors of major CYP or UGT enzymes are unlikely to impact the pharmacokinetics of ponesimod.

In vitro assessments and limited clinical data indicate that the co-administration of ponesimod with strong CYP3A4 and UGT1A1 inducers may decrease the systemic exposure of ponesimod. It is unclear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance. The concomitant use of PONVORY™ with strong CYP3A4 and UGT1A1 inducers is not recommended.

Ponesimod is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3).

M13 is a substrate of OATP1B1, OATP1B3 and BCRP. However, no interaction is expected with inhibitors of these transporters.

Effect of Ponesimod on Other Drugs

Based on *in vitro* data, ponesimod may act as an inhibitor of the efflux transporter BCRP at the intestinal level. This interaction has not been investigated in clinical trials. Caution should be used in the co-administration of ponesimod and drugs that are transported by BCRP.

Ponesimod and its metabolite M13 are not expected to inhibit P-gp, OATP1B1 and OATP1B3, organic anion transporters 1 and 3 (OAT1 and OAT3), organic cation transporters 1 and 2 (OCT1 and OCT2) and multidrug and toxin extrusion transporters 1 and 2 (MATE1 and MATE2-K) at clinically relevant concentrations.

In vitro investigations indicate that ponesimod and its metabolite M13 are not expected to inhibit the activity of CYP (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2 and CYP3A4) and UGT (UGT1A1 and UGT2B7) enzymes or induce the expression of CYP enzymes at the therapeutic dose of 20 mg once daily.

The potential for interaction for M12 has not been investigated as the exposure to this metabolite represents less than 10% of total drug-related exposure at the therapeutic dose of 20 mg once daily.

The drugs listed in Table 5 are based on drug interaction studies.

Table 5: Established or Potential Drug-Drug Interactions

Common name	Source of evidence	Effect	Clinical comment
Atenolol	CT	Atenolol did not affect the PK parameters of PONVORY™. Available data indicated that PONVORY™ did not affect the PK of atenolol. Concomitant treatment resulted in a stronger and prolonged heart rate reduction compared to PONVORY™	Concomitant use should be with caution (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)
Diltiazem	CT	Diltiazem did not affect the PK parameters of PONVORY™. Available data indicated that PONVORY™ did not affect the PK of diltiazem. Concomitant treatment resulted in a slightly less pronounced negative chronotropic response compared to PONVORY™	Concomitant use should be with (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)
Propranolol	CT	No clinically relevant changes in PK of PONVORY™, propranolol, or 4-hydroxypropranolol. Concomitant administration with propranolol once daily at steady state resulted in an additive effect on heart rate	Concomitant use should be with caution (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)
Oral Contraceptive (Ethinyl estradiol (EE) and norethindrone (NE))	CT	PONVORY™ had no effect on EE exposure; NE C_{max} and AUC decreased by 13% and 16%, respectively.	Concomitant use of PONVORY™ is not expected to decrease the efficacy of hormonal contraceptives.
Strong CYP3A and UGT1A1 inducers (e.g. rifampin, phenytoin, carbamazepine)	C	The AUC of PONVORY™ may be reduced with co-administration of strong PXR agonists.	Concomitant use with PONVORY™ is not recommended.
BCRP substrates	T	Based on *in vitro* data, ponesimod has the potential to inhibit BCRP at the intestinal level. The systemic exposure to medications that are	Concomitant use should be with caution.

Common name	Source of evidence	Effect	Clinical comment
Chemotherapy agents (e.g. methotrexate, camptothecin derivatives) Tyrosine kinase inhibitors Rosuvastatin and sulfasalazine		substrates of this transporter may be increased with concomitant use of PONVORY.	

C = Case Study; CT = Clinical Trial; T = Theoretical

Anti-neoplastic, Immune-modulating, or Immunosuppressive Therapies

PONVORY™ has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. PONVORY™ is contraindicated in patients who are immunocompromised while on these therapies. Caution should be used when administering PONVORY™ in the weeks following the administration of these drugs (see 7 WARNINGS AND PRECAUTIONS, Immune, Risk of Infections).

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive effects on the immune system (see 7 WARNINGS AND PRECAUTIONS, Immune, Unintended Additive Immunosuppressive Effects from Prior treatment with Immunosuppressive or Immune-modulating Therapies).

Anti-arrhythmic Drugs and Other QTc-Prolonging Drugs

In a thorough QT interval study, supratherapeutic doses of 40 and 100 mg as tablets in healthy subjects, PONVORY™ was associated with QTc prolongation (see 10 CLINICAL PHARMACOLOGY, Effect on QT/QTc Interval and Cardiac Electrophysiology). PONVORY™ has not been studied in patients taking QT prolonging drugs. Class Ia antiarrhythmics (e.g., procainamide, disopyramide) and Class III antiarrhythmics (e.g., amiodarone, sotalol) may prolong the QTc interval and have been associated with cases of Torsade de Pointes and these drugs were excluded from use in multiple sclerosis clinical trials. Since initiation of PONVORY™ treatment results in both a decreased heart rate and a prolongation of QTc interval, the use of PONVORY™ with such drugs should be avoided. If treatment with PONVORY™ is considered, such patients should be evaluated by a cardiologist prior to initiation of treatment to assess suitability and to determine the most appropriate monitoring, which may include overnight (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In addition to the Class Ia and Class III antiarrhythmic drugs, other drugs that have been associated with QTc interval prolongation and/or Torsade de Pointes, current information sources should be consulted for more comprehensive lists of QTc-prolonging drugs.

Heart Rate-Lowering Drugs

Initiation of treatment with PONVORY™ causes a transient decrease in heart rate and atrioventricular conduction delays. For patients taking drugs that decrease heart rate, treatment

with PONVORY™ should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate (e.g. antiarrhythmics, beta blockers, calcium channel blockers) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Beta-Blockers

Bradyarrhythmic effects are more pronounced when PONVORY™ is added to beta-blocker therapy. Caution should be applied when PONVORY™ is initiated in patients receiving treatment with a beta-blocker. For patients receiving a stable dose of a beta blocker, the resting heart rate should be considered before introducing PONVORY™ treatment. Temporary interruption of the beta-blocker treatment may be needed prior to initiation of PONVORY™ (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Treatment Initiation Recommendations). If treatment with PONVORY™ is considered in patients who are under chronic beta-blocker treatment, advice from a cardiologist should be sought prior to initiation of treatment and they should be monitored during treatment initiation according to procedures similar to those recommended for patients with pre-existing Cardiac Conditions (see 7 WARNING AND PRECAUTIONS, Monitoring and Laboratory Tests, First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

In a drug-drug interaction study, the up-titration regimen of ponesimod (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment) was administered to subjects receiving propranolol (80 mg) once daily at steady-state. No significant changes in pharmacokinetics of ponesimod or propranolol were observed.

Compared to ponesimod alone, the combination with propranolol after the first dose of ponesimod (2 mg) had a 12.4 bpm (90% CI: -15.6 to -9.1) decrease in mean hourly heart rate and at the first dose of ponesimod (20 mg) after up-titration a 7.4 bpm (90% CI: -10.9 to -3.9) decrease in mean hourly heart rate.

Vaccines

Vaccinations may be less effective if administered while being treated with PONVORY™ and up to 1 week after its discontinuation.

Avoid the use of live attenuated vaccines while patients are taking PONVORY™. If the use of live attenuated vaccine immunization is required, treatment should be paused from 1 week prior to 4 weeks after a planned vaccination. (see 7 WARNINGS AND PRECAUTIONS, Immune, Risk of Infections).

9.5 Drug-Food Interactions

Food does not have a clinically relevant effect on ponesimod pharmacokinetics, therefore PONVORY™ may be taken with or without food.

9.6 Drug-Herb Interactions

Interaction of ponesimod with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ponesimod is a sphingosine 1-phosphate (S1P) receptor modulator. Ponesimod activates with

high potency the S1P receptor 1 subtype (S1P1).

The binding of ponesimod to S1P1 receptors on lymphocytes prevents lymphocyte egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts its therapeutic effects in multiple sclerosis is unknown but may involve reduction of lymphocyte migration into the central nervous system.

10.2 Pharmacodynamics

Immune system

In healthy volunteers, ponesimod induces a dose-dependent reduction of the peripheral blood lymphocyte count from a single dose of 5 mg onwards, with the greatest reduction observed 6 hours post dose, caused by reversible sequestration of lymphocytes in lymphoid tissues.

After 7 daily doses of 20 mg, the greatest decrease in absolute mean lymphocyte count was to 26% of baseline (650 cells/µL), observed 6 hours after administration. Peripheral blood B cells [CD19+] and T cells [CD3+], T-helper [CD3+CD4+], and T cytotoxic [CD3+CD8+] cell subsets are all affected, while NK cells are not. T helper cells were more sensitive to the effects of ponesimod than T cytotoxic cells.

PK/PD modeling indicates lymphocyte counts returned to the normal range (≥1.0 x 10^9 cells/L) in >90% of healthy subjects within 1 week of stopping therapy. In the development program, peripheral lymphocyte counts returned to the normal range within 1 week after discontinuation of PONVORY™.

Heart Rate and Rhythm

Ponesimod causes a transient dose dependent reduction in heart rate (HR) and AV conduction delays upon treatment initiation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia and Atrioventricular Conduction Delays). The heart rate decreases plateaued at doses greater than or equal to 40 mg, and bradyarrhythmic events (AV blocks) were detected at a higher incidence under PONVORY™ treatment, compared to placebo. This effect starts within the first hour of dosing and is maximal at 2-4 hours post-dose and HR generally returns to pre dose values by 4-5 hours post-dose on Day 1 and the effect diminishes with repeated administration, indicating tolerance.

With the gradual up titration of ponesimod, the HR reduction is less pronounced. There were no second-degree AV blocks of Mobitz type II or higher degree observed.

The decrease in heart rate induced by ponesimod can be reversed by atropine.

Beta-Blockers

The negative chronotropic effect of co administration of ponesimod and propranolol was evaluated in a dedicated pharmacodynamics safety study. The addition of ponesimod to propranolol at steady state has an additive effect on HR effect. The largest difference in mean maximum difference in mean hourly HR from time-matched baseline (E_{max}HR) between the combination of ponesimod with propranolol compared to ponesimod alone was -12.4 bpm (90% CI: -15.61 to -9.14 bpm) and this was observed on the first dose of ponesimod 2 mg plus 80 mg propranolol at steady-state. The difference between treatments decreased with subsequent doses reaching -7.4 bpm (90% CI: -10.89 to -3.88 bpm) on the first 20 mg dose of ponesimod (after up-titration) plus steady-state propranolol. The lowest value of the mean of the minimum of the mean hourly HR (HR_{nadir}) in the combination arm was 48.9 bpm (95% CI: 46.43 to 51.27 bpm) observed on the third day of the ponesimod (3 mg) up-titration regimen and increased to 54.1 bpm (51.72 to 56.53 bpm) on first 20 mg dose of ponesimod.

Effect on QT/QTc Interval and Cardiac Electrophysiology

In a randomized, double-blind, parallel group, placebo- and positive-controlled multiple dose ECG assessment study in healthy adult subjects (58 subjects per treatment group), ponesimod was administered orally according to the following multiple dose up-titration; 10 mg on Days 2–4, 20 mg on Days 5-7, 40 mg on Days 8-12, 60 mg on Days 13-15, 80 mg on Days 16-18, and 100 mg on Days 19-23. Ponesimod increased the placebo-corrected baseline-adjusted mean QTcI (ΔΔQTcI) with a maximum mean effect of 6.9 msec (90% CI 2.5, 11.3) on 40 mg ponesimod and 9.1 ms (90% CI 4.1, 14) on 100 mg ponesimod. The maximum QTc prolongation effect occurred at 2.5 hours post-dose on 40 mg ponesimod and 8 hours post-dose on 100 mg ponesimod. There was no consistent signal of increased incidence of QTcI outliers associated with ponesimod treatment, either as absolute values (QTcI > 480 ms) or change (QTcI increase > 60 ms) from baseline.

The maximum observed reduction in mean HR from baseline of 9 bpm for both vital signs HR and 12-lead ECG HR was observed at 2.5 hours post-dose following the initial ponesimod dose of 10 mg.

Pulmonary Function

Dose dependent reductions in absolute forced expiratory volume over 1 second were observed in ponesimod treated subjects and were greater than in subjects taking placebo (see 7 WARNINGS AND PRECAUTIONS, Respiratory Effects). The effects observed on pulmonary function can be reversed with administration of a short acting beta2 agonist.

10.3 Pharmacokinetics

Table 6- Summary of ponesimod Pharmacokinetic Parameters in healthy control subjects

	C_{max}	T_{max}	$T1/2_{(h)}$	$AUC_{0\text{-}inf}$	CL	Vd
Single dose mean*	91.7 ng/mL	2-4 h	33	1318 h.ng/mL	3.8 L/h	160 L

*C_{max}, T_{max}, T ½ and AUC were obtained from a single dose of 20 mg ponesimod. CL and Vd were determined with a 5 mg i.v. dose of ponesimod.

Absorption: The time to reach maximum plasma concentration of ponesimod is 2-4 hours post-dose. Ponesimod absorption is extensive. The absolute oral bioavailability of a 10 mg dose is 84%.

Following ponesimod oral dosing, C_{max} and AUC increased approximately dose proportionally in the dose range studied (1-75 mg). Steady-state levels are approximately 2.0 to 2.6-fold greater than with a single dose and are achieved following 3 days of administration of the maintenance dose of ponesimod.

The pharmacokinetic profile of ponesimod is characterized by low inter-subject variability, approximately 25% across studies.

The pharmacokinetics of ponesimod is similar in healthy subjects and subjects with multiple sclerosis.

Food Effect

The PK profile of ponesimod was similar under fed and fasted condition. When compared to the fasted state, a slightly higher C_{max} and delayed t_{max} were observed under fed condition, although these differences were not considered clinically significant.

Food does not have a clinically relevant effect on ponesimod pharmacokinetics, therefore PONVORY™ may be taken with or without food.

Distribution: Ponesimod is distributed to body tissues with a moderate mean volume of distribution of 160 L. Ponesimod and M13 are highly bound to plasma proteins (≥ 99%) and are mainly distributed in the plasma fraction of whole blood, with plasma partition coefficient values of 78.5% and virtually 100%, respectively.

Metabolism: Ponesimod is extensively metabolized prior to excretion in humans, though unchanged ponesimod was the main circulating component in plasma. One major metabolite, M13, and one minor metabolite, M12, have also been identified in human plasma, respectively representing 20% and 6% of total drug-related exposure. As both metabolites are more than 10-fold less active than ponesimod in *in vitro* potency assays, neither are expected to contribute meaningfully to activity at the therapeutic dose of ponesimod.

Metabolism of ponesimod to M13 occurs primarily through a combination of non-Cytochrome P450 (CYP450) enzymes. Multiple CYP450 (CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12) and non-CYP450 enzymes catalyze the oxidation of ponesimod to M12. Non-CYP450 enzymes involved in the formation of M12 and M13 have not been conclusively identified. Ponesimod also undergoes direct glucuronidation (mainly via UGT1A1 and UGT2B7, but also via UGT1A3, UGT1A4 and UGT2B4).

Elimination: A systemic clearance of 3.8 L/hour was estimated in healthy subjects. The elimination half-life after oral administration is approximately 33 hours.

Following a single oral administration of ^{14}C-ponesimod, 57% to 80% of the dose was recovered in feces (16% as unchanged ponesimod), and 10% to 18% in urine (no unchanged ponesimod), and 14% and 0.3% of the dose was recovered as M12 in the feces and urine, respectively and 1.7% and <1% of the dose was recovered as M13 in the feces and urine, respectively.

Special Populations and Conditions

- **Pediatrics:** No studies have been performed with PONVORY™ in pediatric patients.
- **Geriatrics:** Results from population pharmacokinetics suggest that there was no significant effect of age on the pharmacokinetics of ponesimod, however clinical studies of ponesimod did not include patients aged 65 and over. PONVORY™ should be used with caution in this population.
- **Sex:** Gender has no clinically significant influence on ponesimod pharmacokinetics.
- **Pregnancy and Breast feeding:** Based on animal studies, PONVORY™ may cause fetal harm. PONVORY™ is contraindicated during pregnancy (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women7.1.2 Breast-feeding).
- **Genetic Polymorphism:** There is no evidence that polymorphism would impact the metabolism of ponesimod from non-clinical studies. Genotyping testing of MS patients is not necessary as there is no major metabolism via polymorphic CYPs.
- **Ethnic Origin:** No clinically relevant pharmacokinetic differences were observed between Japanese and Caucasian subjects.

- **Hepatic Insufficiency/Impairment:**
  A single dose study with ponesimod 10 mg in adult subjects with mild, moderate or severe hepatic impairment (n=8 each; Child-Pugh class A, B and C, respectively), showed no change in ponesimod C_{max}, but ponesimod $AUC_{0-\infty}$ was increased by 1.3-, 2.0- and 3.1-fold respectively compared to healthy subjects. The elimination half-life of ponesimod was also increased 1.5-, 1.8- and 2.6-fold in these groups, respectively.

  Hepatic impairment also altered the PK parameters of the M12 and M13 metabolites compared to healthy subjects. For M12, the elimination $t_{½}$ was approximately 1.5-, 2.1-, and 2.5-fold greater in the mild, moderate, and severe hepatic impairment groups respectively, compared to healthy subjects. This resulted in increased exposure (AUC) to M12 of 1.3-, 4.3-, and 5.6-, respectively. For M13, the elimination half-life was 2.1-, 2.4-, and 3.1-fold greater in mild, moderate, and severe hepatic impairment groups respectively, compared to healthy subjects. This resulted in increased exposure (AUC) to M13 of 1.2-, 1.7-, and 2.1-fold respectively.

  PONVORY™ is contraindicated in patients with moderate and severe hepatic impairment, as the risk of adverse reactions may be greater (see 2 CONTRAINDICATIONS). No dose adjustment is needed in patients with mild hepatic impairment (Child-Pugh class A).

- **Renal Insufficiency/Impairment:**
  A single oral dose study with 10 mg ponesimod in subjects with moderate and severe renal impairment (n=8 for each group) suggests that dose adjustments are not necessary in patients with renal impairment.

  In adult subjects with moderate or severe renal impairment (estimated creatinine clearance (CrCl) as determined by the Cockroft-Gault between 30-59 mL/min for moderate and <30 mL/min for severe), there were no significant changes in ponesimod C_{max} and AUC compared to subjects with normal renal function (CrCl>90 mL/min).

  The effect of dialysis on the PK of ponesimod has not been studied. Due to the high plasma protein binding (greater than 99%) of ponesimod, dialysis is not expected to alter the total and unbound ponesimod concentration and no dose adjustments are anticipated based on these considerations.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30ºC) in the original packaging. Protect from moisture.

PONVORY™ must be used within the shelf-life. See expiry date on the carton of the Initiation Pack and Maintenance Pack.

PONVORY™ must be kept out of the reach and sight of children.

Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

The Initiation and Maintenance Packs have child-lock blister wallets supplied within each carton. Press and hold blister wallets to open blister cards. Fold card and push back into sleeve firmly until locked.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Brand name: PONVORY™

Common name: ponesimod

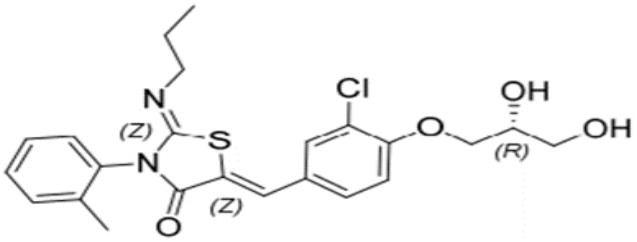
Chemical name: (2*Z*,5*Z*)-5-[3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]benzylidene]-3- (2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one

Molecular formula and molecular mass:

molecular formula: $C_{23}H_{25}ClN_2O_4S$

molecular mass: 460.97 g/mol

Structural formula:



Physicochemical properties: The drug substance is a white to light yellowish color powder with solubility of 0.669µg/mL in water at 20ºC and practically insoluble or insoluble in aqueous media with pH of 1.23 to 12.79

14 CLINICAL TRIALS

The efficacy and safety of PONVORY™ (ponesimod) was demonstrated in the Phase 3 study, OPTIMUM, a multicenter, randomized, double blind, parallel group active-controlled superiority study in patients with relapsing MS treated for 108 weeks (Table 7).

14.1 Trial Design and Study Demographics

Table 7: Summary of Patient Demographics for the OPTIMUM Study in relapsing MS

Study #	Trial design	Dosage, Route of administration and Duration	Study subjects (n)	Mean age (Range)	Sex
AC-058-B301 (OPTIMUM)	Randomized, multicenter, double-blind, parallel group, active-controlled superiority study with teriflunomide as the active comparator.	PONVORY™ 20 mg or teriflunomide 14 mg, Once-daily (oral) for 108 weeks.	Total=1133 PONVORY™ (n=567) Teriflunomide (n=566)	37 years (18-55)	Male: 35% Female: 65%

In OPTIMUM, 1133 patients were randomized to receive either PONVORY™ (N=567) or teriflunomide (N=566), beginning with a 14-day dose titration starting with 2 mg. (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

The study included patients with relapsing course of MS from onset (RRMS or SPMS with superimposed relapses and an Expanded Disability Status Scale (EDSS) score of 0 to 5.5, having experienced at least one relapse within the prior year, or two relapses within the prior two years, or having at least one gadolinium-enhancing (Gd+) lesion on a brain MRI within the prior 6 months or at baseline.

The mean (median) time since first MS symptoms to randomization in the study was 7.6 (5.7) years, and the baseline demographic and disease characteristics were balanced between the treatment groups (Table 8).

The mean treatment exposure was 96.7 weeks for PONVORY™ -treated patients and 97.5 weeks for the teriflunomide treated patients.

Table 8: Key Baseline Characteristics, Full Analysis Set

Characteristics	PONVORY™ N=567	Teriflunomide N=566
Baseline EDSS (mean)	2.57 (SD 1.17)	2.56 (SD 1.22)
Number of relapses in last year prior to study entry (mean)	1.2	1.3
Any DMT* received within 2 years prior to randomization • Yes • No	 37.6% 62.4%	 37.3% 62.7%
Presence of Gd+T1 lesions at baseline	39.9%	45.4%
Presence of T2 lesions at baseline • <9 • ≥9	 11% 89%	 8% 92%

Characteristics	PONVORY™ N=567	Teriflunomide N=566
Mean time since most recent relapse (months) at screening (Min, Max)	5.4 (0.2, 44.9)	5.0 (0.3, 26.2)
Multiple Sclerosis subtype • RRMS • SPMS with superimposed relapses	 97.4% 2.6%	 97.5% 2.5%
Highly active disease#	35.6%	35.3%

*DMT= MS disease modifying agent; SD=standard deviation

A subject was considered to have highly active disease if one or both of the following conditions were fulfilled:

1) Any DMT for MS received within 12 months prior to randomization and one or both of the following:
   - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions
   - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for subjects with at least one relapse within 2 years prior to study entry.
2) ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion

Neurological evaluations were performed every 12 weeks as well as at the time of a suspected relapse. Brain MRIs were performed at baseline and at Weeks 60 and 108. Of the randomized patients, 86.4% of PONVORY™ -treated patients and 87.5% of teriflunomide treated patients completed the study as per protocol.

The primary endpoint of the study was the annualized relapse rate (ARR) from baseline up to end of study (EOS).

The pre-specified hierarchical fallback testing sequence included the primary endpoint and the following secondary endpoints:

1) Change from baseline to Week 108 in fatigue-related symptoms as measured by the **Symptoms domain** of the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ–RMS).

2) Cumulative number of combined unique active lesions (CUALs, defined as new Gd+ T1 lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to Week 108.

3) Time to 12-week confirmed disability accumulation (CDA) from baseline to EOS. A 12-week CDA was defined as an increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, which was confirmed after 12 weeks.

4) Time to 24-week CDA from baseline to EOS.

Other MRI-based exploratory efficacy endpoints, including percent change in brain volume, were analyzed without correction for multiplicity or hierarchical testing.

14.2 Study Results

Results are presented in Table 9.

Table 9: Results of the OPTIMUM Study Efficacy

	PONVORY™	Teriflunomide
	N=567	N=566
Annualized Relapse Rate		
Mean Annualized Relapse Rate[a]	0.202	0.290
Relative ARR reduction	30.5% (p=0.0003)*	
Patients with at least one confirmed relapse	29.3%	39.4%
Fatigue Symptoms Score	N=449	N=458
Mean change from Baseline in FSIQ-RMS[b] Symptoms to Week 108	−0.01	3.56
Mean difference	−3.57 (p=0.0019)*	
Cumulative number of Combined Unique Active Lesions (CUALs)	N=539	N=536
Mean number of CUALs per year[c]	1.41	3.16
Relative Rate reduction	56% (p<0.0001)*	
Brain volume	N=436	N=434
Mean % change from Baseline to Week 108 in brain volume[d]	-0.91%	-1.25%
Mean difference	0.34%#*	
Confirmed Disability Accumulation (CDA)	N=567	N=566
Patients[e] with first 12-week CDA	10.8%	13.2%
Relative risk reduction[f]	17% (p = NS)	
Patients[e] with first 24-week CDA	8.7%	10.5%
Relative risk reduction[f]	16% (p = NS)	

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

[a] Defined as confirmed relapses per year up to EOS (Negative binomial regression model with stratification variables (EDSS ≤ 3.5 versus EDSS > 3.5; DMT 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] Fatigue Symptoms and Impact Questionnaire – Relapsing Multiple Sclerosis (FSIQ–RMS), assessed over a 7-day period on a scale normalized from 0-100. A negative change from baseline indicates an improvement in fatigue symptoms

[c] Defined as new Gd+ T1 lesions plus new or enlarging T2 lesions [without double counting of lesions] per year from baseline to Week 108 (Negative binomial regression model with stratification factors and Gd+ T1 lesions (present/absent) at baseline as covariates)

[d] Mixed Effect Model with linear time effect adjusted for stratification factors, GD+ T1 lesions (present/absent) and normalized brain volume at baseline

[e] Based on time to first 12-Week/24-Week CDA event up to Week 108 (Kaplan-Meier estimates)

[f] Defined as time to 12-Week/24-Week CDA from baseline to EOS (Stratified Cox proportional hazard model, p value based on the stratified log rank test)

* Statistically significant, according to the predefined multiplicity testing strategy

p=NS: not statistically significant, treatment comparisons: Relative rate/risk (PONVORY™ vs Teriflunomide) and Mean difference (PONVORY™ - Teriflunomide).

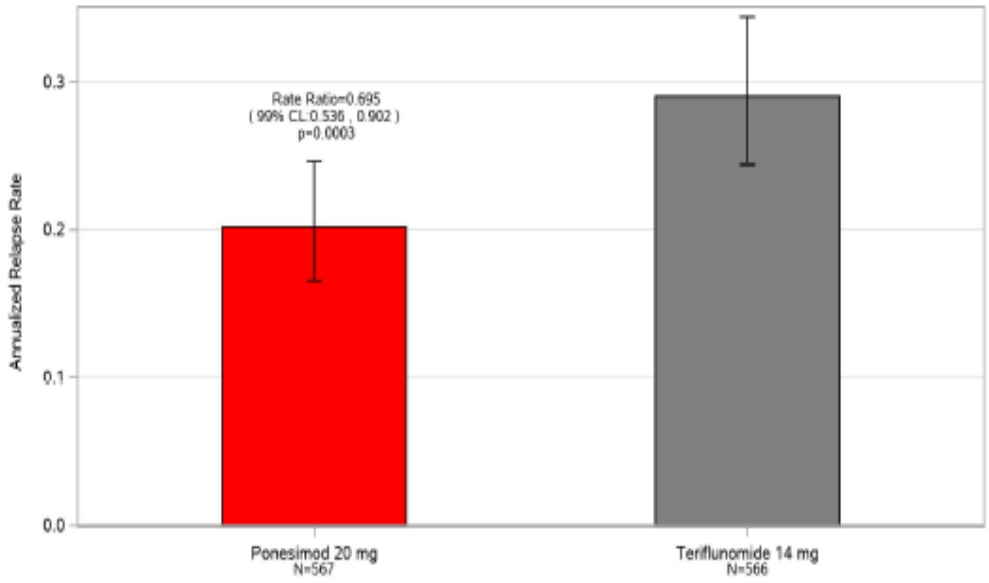
Nominally statistically significant (nominal p-value <0.0001)

Primary Endpoint:

Annualized Relapse Rate

PONVORY™ was statistically significantly superior to teriflunomide in relative reduction of the annualized relapse rate (ARR) up to EOS by 30.5% (p=0.0003) (Figure 1).

Figure 1: Confirmed Relapses up to End of Study- Annualized Relapse Rate from Negative Binomial Regression (Full Analysis Set)



ARR=annualized relapse rate (confirmed relapses per year), rate ratio: ponesimod vs. teriflunomide.
Negative binomial model is applied with Wald confidence limits and p-value.
Offset: log time (years) up to EOS.
Covariates: EDSS strata (<=2.5,>2.5), DMT in last 2 years prior to randomization strata (Y,N), number of relapses in year prior study entry (<=1, >=2).

Secondary Endpoints:

Change from Baseline to Week 108 in Fatigue related Symptoms (FSIQ–RMS)

The FSIQ-RMS symptoms domain (FSIQ-RMS-S) consists of 7 items with a recall of 24 hours measured on an 11-point numeric rating scale, ranging from 0 = "Not at all" to 10 = "Very Severe". Data are collected over 7 consecutive days to assess fatigue related symptoms. Standardized scores range from 0 to 100, with a higher score indicating greater fatigue.

The secondary endpoint of change from baseline to Week 108 in the **Symptoms** domain of the FSIQ-RMS, showed PONVORY™ had a superior effect compared to teriflunomide at Week 108 on fatigue **symptoms** mean difference: −3.57 [95% CLs: −5.83, −1.32]; the difference was statistically significant with p=0.0019.

The FSIQ-RMS impacts domain (FSIQ-RMS-I) consists of 13 items that assess impacts of fatigue-related symptoms in three subdomains: physical impacts, cognitive and emotional impacts, and coping impacts. The instrument has a recall period of 7 days with items measured on a 5-point Likert scale, ranging from no impact (0) to extreme impact (4). Scores for the three FSIQ-RMS-I domains are standardized to range from 0 to 100 with higher scores indicating greater impact.

Exploratory analyses using the change from baseline to Week 108 in fatigue-related **Impact** scores as measured by the **impact** domain of the FSIQ–RMS showed that the LS mean difference (PONVORY™ 20 mg − teriflunomide 14 mg) in change from baseline to Week 108 for the physical impact subdomain was not significant with a mean difference of −2.31 (95% CLs: −5.26, 0.64; p=0.1247); the cognitive/emotional impact subdomain was also not significant with a mean

difference of −2.43 (95% CLs: −4.93, 0.07; p=0.0568); and the coping impact subdomain, was significant with a mean difference of −2.94 (95% CLs: −5.86, −0.01; p=0.0489).

Cumulative number of CUALs, from baseline to Week 108
PONVORY™ was statistically significantly superior to teriflunomide in reducing the relative rate of CUALs on brain MRIs from baseline to Week 108 by 56% (p<0.0001).

Confirmed Disability Accumulation
PONVORY™ reduced the risk of 12- and 24-week CDA by 17% and 16% respectively, compared to teriflunomide, however the difference did not reach statistical significance.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Repeat-dose Toxicity

In the lung, pulmonary histiocytosis and lung weight increase were observed in mice, rats, and dogs after treatment with ponesimod. These findings are considered secondary to increased vascular permeability caused by S1P1 receptor modulation. The no observed adverse effect levels (NOAELs) for lung findings were identified in rat and dog 4-week toxicity studies and were associated with AUC_{0-24} and C_{max} values similar or inferior to human total and peak systemic exposures following recommended human dose (RHD) of 20 mg/day.

In the heart of the dog, arterial lesions were observed in the posterior papillary muscles of the left ventricle, after 13, 26, and 52 weeks of treatment at ≥5 mg/kg/day. The finding is considered secondary to hemodynamic changes and the dog is known to be sensitive to ponesimod-related hemodynamic changes in the heart. When compared with human systemic exposures at RHD of 20 mg/day the NOAEL in the dog was 4.3 and 6.2 times the human systemic exposures based on $AUC_{0–24}$ and C_{max}, respectively.

Carcinogenicity and Genotoxicity: Oral carcinogenicity studies of ponesimod were conducted in mice and rats. In rats, ponesimod was administered at oral doses of 3, 10 and 30 mg/kg/day in males and 10, 30 and 100 mg/kg/day in females for up to 2 years.

Ponesimod did not induce neoplastic lesions. The highest doses tested (30/100 mg/kg/day) are 3.6 and 18.7 times the human systemic exposures at RHD of 20 mg/day based on the steady state clinical AUC_{0-24}.

In mice, ponesimod was administered at oral doses of 50, 150 and 400 mg/kg/day in males and 30, 100 and 300 mg/kg/day in females for up to 2 years. The incidence of combined hemangiosarcoma and hemangioma was increased in males in all treated dose levels and females at the high dose level. A no-observed-effect-level (NOEL) for carcinogenesis was not established in males and was the lowest dose in females. The AUC_{0-24} for males and females at the lowest doses tested (50 and 30 mg/kg/day respectively) are 4.9 and 2.4 times the human systemic exposures at RHD of 20 mg/day.

Ponesimod was negative in a battery of in vitro (Ames, chromosomal aberration in mammalian

cells) and in vivo (micronucleus in rat) assays.

Reproductive and Developmental Toxicology: When ponesimod was orally administered (1, 10 and 40 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-fetal survival, growth, and morphological development were severely compromised at 40 mg/kg/day.

Teratogenic effects with major skeletal and visceral abnormalities were observed at doses ≥ 10 mg/kg/day. A NOAEL for embryo fetal developmental toxicity in rats was established at 1 mg/kg/day. When ponesimod was orally administered (0.25, 1 and 4 mg/kg/day) to pregnant rabbits during the period of organogenesis, a slight increase in post-implantation losses and fetal findings (visceral and skeletal) were noted at 4 mg/kg/day.

The embryo-fetal NOAEL in rabbits was 1 mg/kg/day. The AUC_{0-24} in rats and rabbits at the NOAEL (1 mg/kg/day in both species) are lower than the human systemic exposures at the RHD of 20 mg/day.

When ponesimod was orally administered (5, 10 and 20 mg/kg/day) to female rats throughout pregnancy and lactation, decreased pup survival and body weight gain, and reduced fertility (females only) were observed in the offspring at 20 mg/kg/day only. All ponesimod treated F1 pups had delayed sexual maturation. The AUC_{0-24} at the NOAEL of 10 mg/kg/day is 1.2 to 1.5 times that in humans at the RHD of 20 mg/day.

Fertility

In the male and female fertility studies in rats, mating and fertility were unaffected by treatment at doses up to 100 mg/kg/day. There was no effect on early pregnancy and no effect on sperm parameters. Plasma exposure (AUC) at the NOAEL in the rat was approximately 18 and 31 times (for males and females, respectively) that in humans at the RHD of 20 mg/day.

No effects were observed on male reproductive organs when evaluated histopathologically in repeat dose toxicology studies for up to 26 or 52 weeks in rats or dogs, respectively.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr PONVORY™

ponesimod tablets

Read this carefully before you start taking PONVORY™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PONVORY™.

What is PONVORY™ used for?
PONVORY™ is used to treat adults with relapsing remitting Multiple Sclerosis (RRMS).

How does PONVORY™ work?
PONVORY™ contains ponesimod. Ponesimod binds to certain receptors on your white blood cells. This keeps the white blood cells in your body's lymph nodes and lowers the number of white blood cells circulating in your body. How exactly PONVORY™ works is not known, but it may be due to less white blood cells entering your central nervous system where they could cause inflammation and damage to the protective coating around the nerves in the brain and spinal cord.

What are the ingredients in PONVORY™?
Medicinal ingredient: ponesimod
Non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, silica colloidal anhydrous and sodium laurilsulfate

Tablet coating: Opadry II is used for the tablet coating and includes: hydroxypropyl methylcellulose, lactose monohydrate, polyethylene glycol 3350, titanium dioxide, and triacetin.

In addition, the following strengths include in their tablet coating:
- 3 mg, 4 mg, 7 mg, 8 mg, 9 mg and 10 mg: iron oxide red
- 4 mg, 5 mg, 8 mg and 9 mg: iron oxide black
- 3 mg, 5 mg, 7 mg, 9 mg, 10 mg and 20 mg: iron oxide yellow

PONVORY™ comes in the following dosage forms:
Film-coated tablets

The Initiation Pack contains 14 tablets of <u>different strengths</u> of ponesimod: 2 tablets (2 mg), 2 tablets (3 mg), 2 tablets (4 mg), 1 tablet (5 mg), 1 tablet (6 mg), 1 tablet (7 mg), 1 tablet (8 mg), 1 tablet (9 mg) and 3 tablets (10 mg).

The Maintenance Pack contains <u>only</u> 20 mg tablets of ponesimod.

Do not use PONVORY™ if:
- you are allergic to ponesimod or to any of the other ingredients of PONVORY™ (listed in **What are the ingredients in PONVORY™**)
- you are at an increased risk of opportunistic infection, (i.e. if you have a weakened immune system) due to:

    - treatments that suppress the immune system (cancer treatments, immunosuppressive or immune modulating therapies, total lymphoid irradiation or bone marrow transplants)
    - disease (immunodeficiency syndrome)
- you currently have a severe bacterial, fungal or viral infection (such as hepatitis or tuberculosis)
- you currently have cancer (except for a type of skin cancer called basal cell carcinoma)
- if you have had in the last 6 months:
    - a heart attack
    - unstable angina
    - stroke or warning signs of a stroke
    - a sudden worsening of the signs and symptoms of heart failure that required treatment or you have been diagnosed with Class III or IV heart failure or certain types of heart failure
- you have or have had a history of certain types of irregular or abnormal heartbeat (arrhythmia) and do not have a pacemaker
- you have liver problems
- you are pregnant, think you may be pregnant or plan to get pregnant
- you are of childbearing age and not using an effective method of birth control

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PONVORY™. Talk about any health conditions or problems you may have, including if you:

- have or had problems with your heart including:
    - an irregular or abnormal heartbeat (arrhythmia) and are taking medicines to treat it
    - a heart attack
    - severe heart disease
    - uncontrolled high blood pressure
    - a history of stroke or other diseases related to blood vessels in the brain
    - have a low resting heart rate
    - an abnormal heart rhythm or at a greater risk of having an abnormal heart rhythm due to an existing condition or factors such as gender and age
    - have low levels of electrolytes (such as potassium, magnesium or calcium), if you are at a higher risk, or you have heart rhythm disturbances or where an electrocardiogram (ECG) shows a prolonged QT interval
- have ever suddenly passed out or fainted
- have trouble breathing
- are taking medicines:
    - to lower your blood pressure
    - to treat an irregular heart beat (medicines that cause QT prolongation)
    - that slow your heart rate
- have a condition where you stop breathing while you sleep (sleep apnea)
- have severe lung disease including chronic obstructive pulmonary disease (COPD)
- have or have had seizures
- have a fever or infection

- have a weakened immune system and are unable to fight infections-due to a disease or from taking medicines that weaken your immune system (such as medicines that suppress or modulate the immune system, including other medicines used to treat MS, and medicines used to treat cancer, including corticosteroids).
- have had chicken pox or have received the chicken pox vaccine.
- have liver problems
- have diabetes
- have eye problems – especially an inflammation of the eye called 'uveitis'
- have high blood pressure.
- are breastfeeding or planning to breastfeed your baby. It is not known if PONVORY™ can pass to your baby through your breast milk.
- you are allergic to lactose

Other warnings you should know about:

Patients taking immunosuppressive or immune modulating medicines: you could be at an increased risk for developing cancer, particularly skin cancer. Basal cell carcinoma, malignant melanoma were reported with patients on PONVORY™ . Your doctor should check for any abnormal skin growths before you start treatment and regularly during your treatment with PONVORY™ especially if you are at a higher risk for skin cancer. During treatment you should:

- check your skin regularly for unusual changes
- limit how much time you are exposed to the sun and UV rays. You should wear protective clothes and regularly apply sunscreen with a high degree of UV protection
- avoid "light therapy." This is a treatment where you are exposed to daylight or some form of light to treat seasonal affective disorder or to treat skin conditions

Risk of Infections: PONVORY™ lowers the number of white blood cells in your blood. This can increase your risk of developing infections. These can be serious and life-threatening. Your doctor should do a blood test to check your white blood cell count before you start treatment, while you are taking PONVORY™ and after you stop treatment. Your white blood cell levels will usually go back to normal within 1-2 weeks of stopping treatment.

If you have a fever, feel tired, have body aches, chills, nausea or vomiting during treatment or 1-2 weeks after your last dose of PONVORY™, call your doctor **right away. Also tell your doctor right away,** if you get any of the following symptoms **during your treatment** with PONVORY™. It could be serious:

- if you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new or unusual symptoms. These may be the symptoms of **progressive multifocal leukoencephalopathy** (PML). This is a rare brain disorder caused by an infection.

- if you have fever, feel like you have a flu, or have a headache along with a stiff neck, sensitivity to light, nausea, and/or confusion. These may be symptoms of **Cryptococcal meningitis** caused by a fungal infection.

- if you have symptoms such as the sudden start of a severe headache, confusion, seizures, changes in your behaviour and changes to your vision. These may be

symptoms of a condition called **posterior reversible encephalopathy syndrome** (PRES).

Herpes Zoster Virus: Cases of herpes viral infections have been reported in patients treated with PONVORY™.

Slow heart rate: PONVORY™ can cause a slow heart rate– especially after you take your first dose. You should have a test to check the electrical activity of your heart called an 'electrocardiogram' (ECG) **before** you take your first dose of PONVORY™.

- If you are at increased risk for side effects due to a slowing of your heart rate, your doctor may ask you to stay at the doctor's office or clinic for at least 4 hours after your first dose.
- You will also have an ECG at the end of the 4 hours. If your ECG is not normal or you still have a very slow or decreasing heart rate, you may need to be monitored for a longer period.

The same may apply if you are restarting PONVORY™ after taking a break in treatment.

Increase in blood pressure: PONVORY™ can cause an increase in your blood pressure. Your doctor should check your blood pressure while you are taking PONVORY™.

Breathing problems: Some people who take PONVORY™ have shortness of breath. Call your doctor **right away** if you have new or worsening breathing problems.

Vaccinations:

- Chickenpox: If you have never had chickenpox or have not been vaccinated against chickenpox (varicella zoster virus). Your doctor will check your antibody levels and may decide to vaccinate you. If you get the vaccine, you will start treatment 1 month after the full course of the vaccination is completed.
- Human Papilloma Virus (HPV): If you have not been vaccinated for the HPV virus your doctor will decide whether you need to be vaccinated against HPV before starting treatment with PONVORY™.

If you are planning to get any other type of vaccine you should not get certain types of vaccines (called "live attenuated vaccines") while you are taking PONVORY™ and for at least 2 weeks after stopping treatment. The use of live attenuated vaccines may increase your risk of infection and other vaccines may be less effective. Your doctor may want you to stop PONVORY™ 1 week before you get a vaccine and for up to 4 weeks after you have received it.

Macular edema: PONVORY™ can cause a problem with your vision called macular edema. The macula is a small area of the retina at the back of the eye. It allows you to see shapes, colours, and details clearly and sharply. PONVORY™ may cause swelling in the macula. It usually happens within the first 6 months of starting treatment, but it can also happen at any time during treatment.

Your doctor should test your vision before you start taking PONVORY™. They should also test your vision any time you notice changes to your eyesight during treatment. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

Be sure to tell your doctor about any changes in your vision and if you notice:

- blurriness or shadows in the center of your vision

- a blind spot in the center of your vision
- sensitivity to light
- unusually colored (tinted) vision

Depression, thoughts of suicide and suicidal behaviour: These behaviours are known to occur in patients with MS. Tell your family if you have symptoms of depression, thoughts of suicide or thoughts about hurting yourself. If you, your caregiver or family members notice changes in your mood contact your doctor **right away.**

Liver problems: PONVORY™ may cause liver problems. Your doctor should do blood tests to check your liver within the first 3 months of starting treatment and regularly during your treatment with PONVORY™. Call your doctor **right away** if you have any of the following symptoms:

- yellowing of your skin or the whites of your eyes
- abnormally dark urine
- unexplained nausea and vomiting
- stomach pain
- feeling tired
- loss of appetite

Pregnancy and Contraception: You must not become pregnant while taking PONVORY™ and for at least 2 weeks after you stop taking it. If you become pregnant while taking PONVORY™, stop taking it and tell your doctor right away. PONVORY™ may harm your unborn baby.

If you are of childbearing age:

- your doctor should perform a pregnancy test to confirm that you are not pregnant **before** you start treatment with PONVORY™

- and you might get pregnant, you should use effective birth control methods during treatment and for at least **2 weeks** after stopping PONVORY™. Ask your doctor about options of effective birth control

Your doctor may enroll you in Janssen's PONVORY Pregnancy Outcomes Enhanced Monitoring (POEM) program. This program is designed to monitor you if you were exposed to PONVORY™ during pregnancy.

After stopping treatment with PONVORY™:

- PONVORY™ will stay in your body for about 1 week after you stop taking it. Your white blood cell count may remain low during this time and for up 1-2 weeks after. The side effects described in this leaflet may still occur.

- your symptoms of MS can return and may become worse compared to before you started treatment or during treatment. Tell your doctor if MS symptoms become worse after you stop taking PONVORY™.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PONVORY™:

- Medicines that treat an irregular heartbeat (medicines that cause QT prolongation)
  - procainamide
  - amiodarone
  - sotalol

- Medicines that slow down your heartbeat such as:
  - beta-blockers (such as atenolol or propranolol)
  - calcium channel blockers (such as verapamil or diltiazem)
  - other medicines that can decrease your heart rate (digoxin)

- Medicines that suppress or modulate the immune system, including other medicines used to treat MS

- Medicines to treat epilepsy such as phenytoin and carbamazepine

- Medicines used to treat tuberculosis such as rifampin

- Medicines used for chemotherapy and to treat cancer such as corticosteroids, methotrexate, camptothecin and tyrosine kinase inhibitors

- Medicines used to lower cholesterol such as rosuvastatin

- Medicines used to rheumatoid arthritis such as sulfasalazine

Vaccines: If you need to receive a vaccine, talk to your doctor first. For more information about vaccines see "**Other warnings you should know about**."

How to take PONVORY™:
You should only be prescribed PONVORY™ by a neurologist who is experienced in the treatment of MS who can discuss the benefits, harms and the safe use PONVORY™ with you.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Before you start PONVORY™:

Your doctor may perform the following:

- an electrocardiogram (ECG) to check for any pre-existing heart conditions
- liver tests if you have not had one within the last 6 months
- a complete blood test if you have not had one in the last 6 months
- a check of your antibody levels for the chickenpox virus (varicella zoster virus) or Human Papilloma Virus (HPV)
- a pregnancy test if you are a woman of childbearing age
- check if you currently have a severe infection
- check your medication history
- have you go for an eye exam

Patients with certain heart conditions or risk factors: If you have certain heart conditions or risk factors the first dose PONVORY™ will have to be taken in your doctor's office or hospital where your heart rate and blood pressure can be monitored (hourly blood pressure and pulse measurements, ECG monitoring) for at least 4 hours.

Usual Adult Dose:

On Days 1 to 14 – Initiation Pack:

- When you start treatment with PONVORY™ you will be given an Initiation Pack. The Initiation Pack contains 14 tablets of different strengths of ponesimod. Over a period of 14 days, you will slowly increase your dose. Carefully follow the directions in the table below and on the Initiation Pack.
- Write down the date on the blister card when you start taking the medicine
- **Only take 1 tablet each day** at about the same time each day**.** Swallow the tablet whole.
- It is important that you take your dose every day. If you miss a dose see "**Missed Dose**" below.
- When you finish the Initiation Pack switch to the Maintenance Pack (Day 15).

Initiation Pack Dosing Instructions

Day	Dose	Tablet Colour	Tablet Marking
1	2 mg	White	"2" on one side and an arch on the other side
2	2 mg	White	"2" on one side and an arch on the other side
3	3 mg	Red	"3" on one side and an arch on the other side
4	3 mg	Red	"3" on one side and an arch on the other side
5	4 mg	Purple	"4" on one side and an arch on the other side
6	4 mg	Purple	"4" on one side and an arch on the other side
7	5 mg	Green	"5" on one side and an arch and an "A" on the other side
8	6 mg	White	"6" on one side and an arch and an "A" on the other side
9	7 mg	Red	"7" on one side and an arch and an "A" on the other side
10	8 mg	Purple	"8" on one side and an arch and an "A" on the other side
11	9 mg	Brown	"9" on one side and an arch and an "A" on the other side
12	10 mg	Orange	"10" on one side and an arch and an "A" on the other side
13	10 mg	Orange	"10" on one side and an arch and an "A" on the other side
14	10 mg	Orange	"10" on one side and an arch and an "A" on the other side

<u>On Day 15 and after – Maintenance Pack Dosing Instructions:</u>

- Start the Maintenance Pack.
- Write down the date on the blister card when you start the Maintenance Pack.
- The recommended dose is 20 mg once a day at about the same time each day. Swallow the tablets whole.
- Continue taking PONVORY™ every day for as long as your doctor tells you. Do not stop taking this medicine without talking to your doctor first.
- It is important that you take your dose every day. If you miss a dose see **"Missed Dose"** below.

Overdose:

If you think you, or a person you are caring for, have taken too much PONVORY™, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
While taking the Initiation Pack or Maintenance Pack if you miss:

- 1, 2 or 3 doses in a row continue with your treatment by taking the first dose that you missed. Take it as soon as you remember. Then finish the Initiation Pack or Maintenance Pack as planned.
- 4 or more doses in a row, you will need to **restart treatment at Day 1 using a new Initiation Pack**. Call your doctor if this happens so that you can get a new Initiation Pack prescribed to you.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using PONVORY™?
These are not all the possible side effects which you may feel when taking PONVORY™. If you experience any side effects not listed here, contact your healthcare professional.

Very common (may affect more than 1 in 10 people):
- infection of the nose, sinuses or throat (cold)
- increased level of liver enzymes in the blood

Common (may affect up to 1 in 10 people):
- a slower than normal heartbeat (bradychardia), especially when you start treatment with PONVORY™
- urinary tract infection
- bronchitis (inflammation of airways of the lungs)
- flu
- itchy, runny or blocked nose
- viral infection of nose, throat or chest

- viral infection
- infected or irritated throat
- sinus infection
- herpes zoster virus infection (shingles)
- depression
- feeling anxious
- difficulty sleeping
- feeling dizzy
- decreased feeling or sensitivity, especially on the skin
- feeling sleepy
- migraine
- spinning sensation (vertigo)
- high blood pressure
- being short of breath
- cough
- indigestion
- back pain
- joint pain
- arm or leg pain
- ligament sprain
- feeling very tired
- fever
- swollen hands, ankles or feet
- chest discomfort
- increased level of a protein in the blood that may indicate an infection or inflammation
- high level of cholesterol in the blood

Uncommon (may affect up to 1 in 100 people):
- swollen joint
- dry mouth
- sinus infection
- hay fever

Tell your doctor if you notice any of the above side effects. These are not all the possible side effects of PONVORY™. Tell your healthcare professional if you have any side effect that bothers you or that does not go away.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Macular edema (swelling and build-up of fluid in the center of the retina): blurry vision, blurry or wavy vision near or in the center of your field of vision,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
colors may appear washed out or faded			
Herpes zoster (chickenpox): rash of small fluid-filled blisters, appearing on reddened skin		✓	
UNCOMMON			
Leukopenia (abnormally low number of lymphocytes – a type of white blood cells): get infections more easily, fever, sore throat or mouth ulcers due to infections		✓	
Atrioventricular block (irregular heartbeat)			✓
RARE			
Bradycardia (abnormally slow heartbeat): feeling dizzy, tired		✓	
Seizures (fit): loss of consciousness with uncontrollable shaking		✓	
Basal cell carcinoma (a type of skin cancer) a type of skin cancer (basal cell carcinoma, or colored skin bump or skin lesion)		✓	
FREQUENCY NOT KNOWN			
Posterior reversible Encephalopathy syndrome (PRES): symptoms may include sudden severe headache, feeling nauseous or throwing up confusion, drowsiness, personality change, paralysis, abnormal speech, convulsions and vision changes			✓
Cryptococcal infections (a type of fungal infection) including cryptococcal meningitis: headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Progressive multifocal leukoencephalopathy (PML), (a rare brain infection): symptoms may include weakness on one side of your body, problems thinking, or vision changes		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15-30ºC) in the original packaging. Protect from moisture.

Do not use PONVORY™ after the expiry date which is stated on the label.

Keep out of reach and sight of children.

Proper disposal:
Medicines should not be discarded in the toilet or household garbage. Follow your local rules for discarding unused medicine. If you are not sure, ask your pharmacist how to throw away medicines you no longer need. This will help to protect the environment.

If you want more information about PONVORY™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html);

- For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at:1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc.
Toronto, Ontario M3C 1L9

Last Revised: Apr 28, 2021

This document provides you with the most current information at the time of printing