▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION

# PONVORY®

# (PONESIMOD)

## 1 NAME OF THE MEDICINE

Ponesimod

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg, 3 mg, 4 mg, 5 mg, 6 mg , 7 mg, 8 mg, 9 mg,10 mg or 20 mg of ponesimod.

Ponesimod is a white to light yellowish colour powder with solubility of 0.669 microgram/ mL in water at 20°C and practically insoluble or insoluble in aqueous media with pH of 1.23 to 12.79.

Excipient with know effect: sugars as lactose.

For the full list of excipients, see Section 6.1 List of Excipients.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

PONVORY is available as round, biconvex, film-coated tablets for oral use. PONVORY contains ponesimod in the following dosage strengths (see Table 1).

**Table 1: Dosage Form and Strengths for PONVORY**

| Tablet Strength | Tablet Color | Tablet Size | Tablet Debossing |
|---|---|---|---|
| 2 mg | White | 5.0 mm | "2" on one side and an arch on the other side. |
| 3 mg | Red | 5.0 mm | "3" on one side and an arch on the other side. |
| 4 mg | Purple | 5.0 mm | "4" on one side and an arch on the other side. |

| | | | |
|---|---|---|---|
| 5 mg | Green | 8.6 mm | "5" on one side and an arch and an "A" on the other side. |
| 6 mg | White | 8.6 mm | "6" on one side and an arch and an "A" on the other side. |
| 7 mg | Red | 8.6 mm | "7" on one side and an arch and an "A" on the other side. |
| 8 mg | Purple | 8.6 mm | "8" on one side and an arch and an "A" on the other side. |
| 9 mg | Brown | 8.6 mm | "9" on one side and an arch and an "A" on the other side. |
| 10 mg | Orange | 8.6 mm | "10" on one side and an arch and an "A" on the other side. |
| 20 mg | Yellow | 8.6 mm | "20" on one side and an arch and an "A" on the other side. |

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

PONVORY is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis.

### Assessments prior to first dose of PONVORY

Before initiation of treatment with PONVORY, assess the following:

**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 Section 4.4 Special Warnings and Precautions for Use - Infections).

**Liver function tests**

Review results of transaminase and bilirubin levels obtained within the last 6 months (see Section 4.4 Special Warnings and Precautions for Use - Liver Injury).

**Pregnancy test**

Before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available (see Section 4.6 Fertility, Pregnancy and Lactation - Contraception).

**Ophthalmic evaluation**

Obtain an evaluation of the fundus, including the macula (see Section 4.4 Special Warnings and Precautions for Use - Macular Oedema).

**Cardiac evaluation**

Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist and first dose monitoring is recommended (see Section 4.2 Dose and Method of Administration - First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions and Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays).

Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions – Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate and Beta-Blockers).

**Current or prior medications**

If patients are taking anti-neoplastic, immune-modulating or immunosuppressive therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with PONVORY (see Section 4.4 Special Warnings and Precautions for Use - Infections and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Anti-Neoplastic, Immune-Modulating or Immunosuppressive Therapies).

**Vaccinations**

Test patients for antibodies to varicella zoster virus (VZV) before initiating PONVORY; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with PONVORY (see Section 4.4 Special Warnings and Precautions for Use - Infections).

## Dosage (dose and interval)

**Treatment initiation**

A treatment initiation pack must be used for patients initiating treatment with PONVORY (see Section 6.5 Nature and Contents of Container). Initiate PONVORY treatment with the 14-day treatment titration; start with one 2 mg tablet orally and progress with the titration schedule outlined in Table 2. (see Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays).

**Table 2: Dose titration regimen**

| Titration day | Daily dose |
|---|---|
| Day 1 and 2 | 2 mg |
| Day 3 and 4 | 3 mg |
| Day 5 and 6 | 4 mg |
| Day 7 | 5 mg |
| Day 8 | 6 mg |
| Day 9 | 7 mg |
| Day 10 | 8 mg |
| Day 11 | 9 mg |
| Day 12, 13 and 14 | 10 mg |

If dose titration is interrupted, missed dose instructions must be followed (see Section 4.2 Dose and Method of Administration - Missed Doses).

**Maintenance dosage**

After dose titration is complete (see Section 4.2 Dose and Method of Administration – Dosage (Dose and Interval) - Treatment Initiation), the recommended maintenance dosage of PONVORY is one 20 mg tablet taken orally once daily.

## 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 Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays and 5.1 Pharmacodynamic Properties - Pharmacodynamic Effects).

**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 4 hours post-dose is less than 45 bpm
- The heart rate 4 hours post-dose is at the lowest value post-dose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 4 hours post-dose shows new onset second-degree or higher AV block

If post-dose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or if ECG 4 hours post-dose shows new onset second degree or higher AV block or QTc greater than or equal to 500 msec, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no 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 Section 4.4 Special Warnings and Precautions for Use - 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 Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays and 4.5 Interactions with Other Medicines and Other Forms of 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Anti-

Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate and Beta-Blockers).

### Missed doses

Interruption during treatment, especially during 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 of the titration regimen (new treatment initiation pack).

During treatment initiation or maintenance, if treatment needs to be reinitiated with Day 1 of the titration regimen, complete first dose monitoring in patients for whom it is recommended (see Section 4.2 Dose and Method of Administration - First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions).

### Method of administration

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

### Special populations

**Paediatric patients (younger than 18 years of age)**

The safety and efficacy of PONVORY have not been established in paediatric patients younger than 18 years of age.

**Elderly (65 years of age and older)**

Clinical studies of ponesimod did not include patients aged 65 years and over to determine whether they respond differently from younger subjects, therefore PONVORY should be used with caution in this population (see Section 5.2 Pharmacokinetic Properties - Special Populations, Age).

**Renal impairment**

Based on clinical pharmacology studies, no dose adjustment is needed in patients with mild to severe renal impairment (see Section 5.2 Pharmacokinetic Properties - Special Populations, Renal impairment).

**Hepatic impairment**

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) (see Section 4.4, Special Warnings and Precautions for Use – Liver injury and 5.2 Pharmacokinetic Properties - Special populations, Hepatic impairment).

Based on clinical pharmacology studies in adult subjects with moderate or severe hepatic impairment, ponesimod $AUC_{0-\infty}$ was increased 2.0 and 3.1 fold respectively, compared to healthy subjects. PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively), as the risk of adverse reactions may be greater (see Section 4.4 Special Warnings and Precautions for Use – Liver injury and Section 5.2 Pharmacokinetic Properties - Special Populations, Hepatic impairment).

## 4.3 CONTRAINDICATIONS

PONVORY is contraindicated:

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

- In patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation, or Class III or IV heart failure.
- In patients who have presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (see Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays).
- During pregnancy and in women of childbearing potential not using highly effective contraception (see Section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy, Contraception).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Infections

**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 sphingosine 1-phosphate (S1P) receptor modulators.

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.

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 Section 4.4 Special Warnings and Precautions for Use - Reversibility of Immune System Effects After Stopping PONVORY).

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with PONVORY should be considered if a patient develops a serious infection.

*Herpes viral infections*

Cases of herpes viral infection have been reported in the development program of PONVORY.

Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating PONVORY (see Vaccinations below).

*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 magnetic resonance imaging (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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions – Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies).

**Vaccinations**

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against 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 may be less effective if administered during PONVORY treatment.

Avoid the use of live attenuated vaccines 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Vaccines).

## Macular oedema

PONVORY increases the risk of macular oedema. 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.

In the clinical trial experience in patients with all doses of ponesimod, the rate of macular oedema was 0.7%. Most cases occurred within the first 6 months of therapy.

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

**Macular oedema in patients with a history of uveitis or diabetes mellitus**

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular oedema 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.

### 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 Section 4.2 Dose and Method of Administration – Dosage (dose and internal), 5.1 Pharmacodynamic Properties- Pharmacodynamic Effects - Heart Rate and Rhythm).

PONVORY was not studied in patients who had:

- Myocardial infarction or unstable ischaemic heart disease in the last 6 months
- Cardiac failure (New York Heart Association class III-IV) or presence of any severe cardiac disease
- Cardiac conduction or rhythm disorders (including sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest) either in history or observed at screening
- Mobitz Type II second degree AV block or higher-grade AV block observed at screening
- QTcF interval greater than 470 ms (females), and greater than 450 ms (males) observed at screening

**Reduction in heart rate**

After the first dose of PONVORY, the decrease in heart rate 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. 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.

**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 HR during dose titration (see Section 4.8 Adverse Effects (Undesirable Effects)).

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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Anti-Arrhythmic Drugs, QT Prolonging drugs, Drugs That May Decrease Heart Rate).
- In patients with unstable ischaemic 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.
- In patients with a history of Mobitz Type II second degree AV block or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block (see Section 4.3 Contraindications).

**Treatment initiation recommendations**

- Obtain an ECG in all patients to determine whether pre-existing conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of PONVORY treatment to mitigate cardiac effects (see Section 4.2 Dose and Method of Administration - Dosage (Dose and Interval)).

- 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 Section 4.2 Dose and Method of Administration - Assessments Prior to First Dose of PONVORY, 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), or uncontrolled hypertension, 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. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.
    - 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 greater than 55 bpm under chronic beta-blocker treatment, PONVORY can be introduced. If resting heart rate is less than or equal to 55 bpm, beta-blocker treatment should be interrupted until the baseline heart rate is greater than 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Beta-Blockers).
    - 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 Section 4.2 Dose and Method of Administration - First Dose Monitoring in Patients with Certain Pre-existing Cardiac Conditions and 4.5 Interactions with Other Medicines and Other Forms of Interactions - Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate).

**Missed dose during treatment initiation or maintenance treatment**

If 4 or more consecutive daily doses are missed during treatment initiation or maintenance treatment, reinitiate Day 1 of the dose titration (new treatment initiation pack) and follow titration monitoring recommendations (see Section 4.2 Dose and Method of Administration - Missed Doses).

## Respiratory effects

Dose-dependent reductions in forced expiratory volume over 1 second ($FEV_1$) and reductions in diffusion lung capacity for carbon monoxide ($DL_{CO}$) were observed in PONVORY-treated patients mostly occurring in the first month after treatment initiation. In the OPTIMUM study, the reduction from baseline in percent predicted $FEV_1$ at 2 years was 8.3% in PONVORY-treated patients compared to 4.4% in patients receiving teriflunomide 14 mg. The changes in $FEV_1$ and $DL_{CO}$ appear to be partially reversible after treatment

discontinuation. In the OPTIMUM study, 7 patients discontinued PONVORY because of pulmonary adverse events. PONVORY has been tested in MS patients with mild to moderate asthma or chronic obstructive pulmonary disease. The changes in $FEV_1$ 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. Spirometric evaluation of respiratory function should be performed during therapy with PONVORY if clinically indicated.

### Liver injury

Elevations of transaminases 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. Patients should be monitored periodically whilst on treatment.

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 14 mg, respectively. ALT increased eight times ULN in 0.7% PONVORY-treated patients compared to 2.1% in patients receiving teriflunomide 14 mg. The majority of elevations occurred within 6 to 12 months of starting treatment. ALT levels returned to normal after discontinuation of PONVORY. 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.

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively) (see Section 4.2 Dose and Method of Adminsitration - Special Populations, Hepatic impairment and Section 5.2 Pharmacokinetic Properties - Special Populations, Hepatic impairment).

### Increased blood pressure

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. Blood pressure should be monitored during treatment with PONVORY and managed appropriately.

### Skin malignancies

As there is a potential risk of skin malignancies (see section 4.8 Adverse Effects (Undesirable Effects)), patients treated with ponesimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

### Fetal risk

Based on animal studies, PONVORY may cause fetal harm. Due to the risk to the fetus, PONVORY is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraception (see Section 4.3 Contraindications and 4.6 Fertility, Pregnancy and Lactation). 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.

### 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, behavioural 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 ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, PONVORY should be discontinued.

### Unintended additive immunosuppressive effects from prior treatment with immune-modulating or immunosuppressive 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.

### 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.

### 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 Section 5.1 Pharmacodynamic Properties - Pharmacodynamic Effects - Immune System). In the 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.

### Use in elderly

Refer to Section 4.2 Dose and Method of Administration.

### Use in paediatric

Refer to Section 4.2 Dose and Method of Administration

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### Anti-neoplastic, immune-modulating, or immunosuppressive therapies

PONVORY has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration (see Section 4.4 Special Warnings and Precautions for Use - 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 Section 4.4 Special Warnings and Precautions for Use – Prior and Concomitant Treatment With Anti-neoplastic, Immune-Modulating or Immunosuppressive Therapies).

### Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate

PONVORY has not been studied in patients taking QT prolonging drugs.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with PONVORY is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with PONVORY should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., digoxin) (see Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays and 4.5 Interactions with Other Medicines and Other Forms of Interactions - Beta-Blockers). If treatment with PONVORY is considered, advice from a cardiologist should be sought regarding the potential need to switch medications that have heart rate lowering effects and how to best monitor patients during treatment initiation.

### Beta-blockers

Caution should be applied when PONVORY is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of PONVORY (see Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays). Beta-blocker treatment can be initiated in patients receiving stable doses of PONVORY.

In a drug-drug interaction study, the up-titration regimen of ponesimod (see Section 4.2 Dose and Method of Administration – Dosage (Dose and Interval)) 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 (see Section 4.4 Special Warnings and Precautions for Use - Infection).

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during PONVORY treatment and up to 1 week after its discontinuation of treatment with PONVORY (see Section 4.4 Special Warnings and Precautions for Use - Infection).

### Effect of other drugs on ponesimod

*In vitro* studies with human liver preparations indicate that metabolism of ponesimod occurs through multiple, distinct enzyme systems, including multiple CYP450 (CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12), UGT (mainly UGT1A1 and UGT2B7) and non-CYP450 oxidative enzymes, without major contribution by any single enzyme.

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

Co administration of PONVORY 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.

Ponesimod is not a substrate of P gp, BCRP, OATP1B1 or OATP1B3 transporters. Drugs that are inhibitors of these transporters are unlikely to impact the PK of ponesimod.

### Effect of ponesimod on other drugs

*In vitro* investigations indicate that at the therapeutic dose of 20 mg once daily, ponesimod and its metabolite M13 do not show any clinically relevant drug-drug interaction potential for CYP or UGT enzymes, or transporters.

### Oral contraceptives

Co-administration of ponesimod, with an oral hormonal contraceptive (containing 1 mg norethisterone/norethindrone and 35 micrograms ethinyl estradiol) showed no clinically relevant pharmacokinetic interaction with ponesimod. Therefore, concomitant use of ponesimod is not expected to decrease the efficacy of hormonal contraceptives. No interaction studies have been performed with oral contraceptives containing other progestogens; however, an effect of ponesimod on their exposure is not expected.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

In the male and female fertility studies in rats, mating and fertility were unaffected by treatment at oral doses up to 100 mg/kg/day. There was no effect on early pregnancy. Plasma exposure (AUC) at the no-observed-adverse-effect level (NOAEL) in the rat was approximately 18 and 31 times (for males and females, respectively) that in humans at the maximum-recommended human dose 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.

### Use in Pregnancy – Category D

PONVORY is contraindicated during pregnancy (see Section 4.3 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. Oral reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod induced embryofetal lethality and teratogenicity when given during the period of organogenesis. An increased incidence of fetal malformations of the cardiovascular system (including fused ascending aorta trunk, muscular and membranous ventricular septal defects), limbs (syndactyly, ectrodactyly and malrotated hindlimbs) and eye (microphthalmia) were seen in rats. 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 maximum recommended human dose (MRHD) of 20 mg/day.

When ponesimod was orally administered 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 only. All ponesimod treated F1 pups had delayed sexual maturation. An increased incidence of embryofetal death was seen in pregnant F1 females. The $AUC_{0-24}$ at the NOAEL of 10 mg/kg/day is 1.2 to 1.5 times that in humans at the MRHD of 20 mg/day.

### Contraception

#### Females

PONVORY is contraindicated in women of childbearing potential not using highly effective contraception (see Section 4.3 Contraindications). Before initiation of PONVORY treatment in women of childbearing potential, a negative pregnancy test result must be available, and women should be counselled on the potential for a serious risk to the fetus and the need for highly effective contraception during treatment with PONVORY (see Section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy). 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 Section 4.4 Special Warnings and Precautions for Use - Fetal Risk).

### Use in Lactation

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. When ponesimod was orally administered to female rats during pregnancy and lactation, ponesimod was detected in the plasma of the offspring (suggesting excretion of ponesimod in milk), adverse effects on postnatal survival, pup growth and the fertility of female offspring was compromised (see Section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy).

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

## 4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

PONVORY has no or negligible influence on the ability to drive and use machines.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of ponesimod based on the comprehensive assessment of the available adverse event information. A causal relationship with ponesimod cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 1438 MS patients have received PONVORY at doses of at least 2 mg daily. These patients were included in the OPTIMUM (2-year active-controlled versus teriflunomide 14 mg) study (see Section 5.1 Pharmacodynamic Properties - Clinical Trials) and in a Phase 2 (6-month placebo-controlled) study in patients with MS and their uncontrolled extension studies.

In OPTIMUM, 82% of PONVORY-treated patients completed 2-years of study treatment, compared to 82.2% of patients receiving teriflunomide 14 mg. Adverse events led to discontinuation of treatment in 8.7% of PONVORY-treated patients, compared to 6.0% of patients receiving teriflunomide 14 mg. The most common adverse reactions (incidence at least 10%) in PONVORY-treated patients in OPTIMUM were alanine aminotransferase increased, nasopharyngitis, and upper respiratory tract infection.

Table 3 lists adverse reactions that occurred in at least 2% of PONVORY-treated patients and at a higher rate than in patients receiving teriflunomide 14 mg (rounded percentages are presented in the table). Adverse reactions are also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

**Table 3: Adverse Reactions Reported in Phase 3 OPTIMUM Study (Occurring in at Least 2% of PONVORY-Treated Patients and at a Higher Rate Than in Patients Receiving Teriflunomide 14 mg[a])**

| **System Organ Class**<br><br>**Adverse Reaction** | **PONVORY**<br>**N=565**<br>**(%)** | **Teriflunomide 14 mg**<br>**N=566**<br>**(%)** |
|---|---|---|
| **Infections and infestations** | | |
| Nasopharyngitis | 19 | 17 |
| Upper respiratory tract infection | 11 | 10 |
| Urinary tract infection | 6 | 5 |
| Bronchitis | 5 | 4 |
| Influenza | 4 | 4 |
| Respiratory tract infection viral | 3 | 2 |
| Respiratory tract infection | 3 | 3 |
| Pharyngitis | 2 | 2 |
| **Metabolism and nutrition disorders** | | |
| Hypercholesterolemia | 2 | 1 |

| | | |
|---|---|---|
| **Psychiatric disorders** | | |
| Anxiety | 3 | 3 |
| **Nervous system disorders** | | |
| Dizziness | 5 | 3 |
| Somnolence | 3 | 2 |
| Hypoesthesia | 2 | 2 |
| **Ear and labyrinth disorders** | | |
| Vertigo | 2 | 1 |
| **Vascular disorders** | | |
| Hypertension | 8 | 8 |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Dyspnea | 5 | 1 |
| Cough | 4 | 2 |
| **Musculoskeletal and connective tissue disorders** | | |
| Pain in extremity | 4 | 3 |
| Arthralgia | 3 | 3 |
| **General disorders and administration site conditions** | | |
| Pyrexia | 2 | 1 |
| **Investigations** | | |
| Alanine aminotransferase increased | 19 | 9 |
| Aspartate aminotransferase increased | 6 | 4 |
| C-reactive protein increased | 2 | 1 |
| Hepatic enzyme increased | 2 | 1 |

[a] Rounded percentages are presented in the table

In OPTIMUM, the following adverse reactions occurred in less than 2% of PONVORY-treated patients but at a rate at least 1% higher than in patients receiving teriflunomide 14 mg: viral infection, herpes zoster, hyperkalemia, laryngitis, lymphocyte count decreased, lymphopenia, macular edema, transaminases increased, and ligament sprain.

In the Phase 2 (placebo-controlled) study, 85.3% of PONVORY-treated patients completed 6-months of study treatment, compared to 90.9% of patients receiving placebo. Adverse events led to discontinuation of treatment in 5.3% of PONVORY-treated patients, compared to 3.3% of patients receiving placebo. 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.

Adverse reactions with PONVORY in the 6-month Phase 2 placebo-controlled study were generally similar to those in the OPTIMUM study. 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 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.

### Infections

In the Phase 3 OPTIMUM study (see Section 5.1 Pharmacodynamic Properties – Clinical Trials), the overall rate of infections was comparable between the PONVORY-treated patients and those receiving teriflunomide 14 mg (54.2% vs 52.1% respectively). Nasopharyngitis and viral infections were more common in PONVORY-treated patients. Serious or severe infections occurred in 1.6% in PONVORY-treated patients compared to 0.9% of patients receiving teriflunomide 14 mg.

In OPTIMUM, the rate of herpetic infections was not different between the PONVORY-treated patients and those receiving teriflunomide 14 mg (4.8%).

### Bradycardia

In the Phase 3 OPTIMUM study (see Section 5.1 Pharmacodynamic Properties – Clinical Trials), bradycardia at treatment initiation (sinus bradycardia/HR less than 50 bpm on ECG on day 1) occurred in 5.8% of PONVORY-treated patients compared to 1.6% of patients receiving teriflunomide 14 mg. 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.

Initiation of PONVORY treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in HR during dose titration. 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 14 mg in the OPTIMUM study. 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.

### 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 14 mg, 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 10.1% of PONVORY-treated patients and in 9.0% of patients receiving teriflunomide 14 mg.

### Macular Oedema

In the OPTIMUM study, macular oedema was reported in 1.1% of PONVORY-treated patients compared to none of the patients receiving teriflunomide 14 mg.

### Hepatic Effects

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 14 mg, respectively. ALT increased eight times ULN in 0.7% PONVORY-treated patients compared to 2.1% in patients receiving

teriflunomide 14 mg. The majority of elevations occurred within 6 to 12 months of starting treatment. ALT levels returned to normal after discontinuation of PONVORY. 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.

### Seizures

In OPTIMUM, cases of seizures were reported in 1.4% of PONVORY-treated patients, compared to 0.2% in patients receiving teriflunomide 14 mg. It is not known whether these events were related to the effects of MS, to PONVORY, or to a combination of both.

### Respiratory effects

Dose-dependent reductions in forced expiratory volume over 1 second ($FEV_1$) were observed in patients treated with PONVORY (see Section 4.4 Special Warnings and Precautions for Use - Respiratory Effects).

### Malignancies

In OPTIMUM, a 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 14 mg. 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. Patients should be informed against exposure to sunlight without protection and avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

### Symptoms and signs

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 AV conduction blocks, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed (see Section 4.4 Special Warnings and Precautions for Use - Bradyarrhythmia and Atrioventricular Conduction Delays, Increased Blood Pressure and Pharmacodynamic Properties - Heart Rate and Rhythm).

### Treatment

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA50

### Mechanism of Action

Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator. Ponesimod binds with high affinity to S1P receptor 1, which is expressed on a range of cell types including lymphocytes.

Ponesimod blocks the capacity of lymphocytes to egress from lymph nodes reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis may involve reduction of lymphocyte migration into the central nervous system.

### Pharmacodynamic effects

#### 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/microlitre), 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 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 Section 4.4 Special Warnings and Precautions for Use - 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 and no second degree AV blocks of Mobitz type II or higher degree were 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 (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions – Beta-Blockers).

**Effect on QT/QTc interval and cardiac electrophysiology**

In a thorough QT study of supra-therapeutic doses of 40 mg and 100 mg (2- and 5-fold respectively, the recommended maintenance dose) ponesimod at steady-state, ponesimod treatment resulted in mild prolongation of individually corrected QT (QTcI) interval, with the upper bound of 90% two-sided confidence interval (CI) at 11.3 ms (40 mg) and 14.0 ms (100 mg). There was no consistent signal of increased incidence of QTcI outliers associated with ponesimod treatment, either as absolute values or change from baseline. Based on the concentration-effect relationship, no clinically relevant effect on QTc interval is expected for the therapeutic dose of 20 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 Section 4.4 Special Warnings and Precautions for Use - Respiratory Effects). These effects can be reversed with administration of a short acting $beta_2$ agonist.

## Clinical trials

The efficacy of PONVORY was evaluated in the Phase 3 study, OPTIMUM, a multicentre, randomised, double blind, parallel group active controlled superiority study in patients with relapsing MS (RMS) treated for 108 weeks. 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.

Patients were randomised to receive either once daily PONVORY or teriflunomide 14 mg, beginning with a 14-day dose titration (see Section 4.2 Dose and Method of Administration –Dosage (Dose and Internal)). 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.

The primary endpoint of the study was the annualised relapse rate (ARR) from baseline up to end of study (EOS). The prespecified hierarchical fallback testing sequence included the primary endpoint and the secondary endpoints: cumulative number of combined unique active lesions (CUAL, defined as new Gd+ T1 lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to Week 108; time to 12-week confirmed disability accumulation (CDA) from baseline to EOS; and time to 24-week 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, or an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score ≥5.5 which was confirmed after 12 weeks.

In OPTIMUM, 1133 patients were randomised to either PONVORY (N=567) or teriflunomide 14 mg (N=566); 86.4% of PONVORY-treated patients and 87.5% of teriflunomide 14 mg-treated patients completed the study as per protocol. The baseline demographic and disease characteristics were balanced between the treatment groups. At baseline, the mean age of patients was 37 years (standard deviation 8.74), 97% were white and 65% were female. The mean disease duration was 7.6 years, the mean number of relapses in the previous year was 1.3, and the mean EDSS score was 2.6; 57% of patients had not received any prior disease-modifying treatments (DMT) for MS. At baseline, 40% of PONVORY-treated patients had one or more Gd+ T1 lesions on brain MRI (mean 1.9).

Results are presented in Table 4. Analysis of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy

of PONVORY on the primary and secondary endpoints was consistent with the overall population.

**Table 4: OPTIMUM Study Efficacy Results**

| | **PONVORY** | **Teriflunomide 14 mg** |
|---|---|---|
| Clinical Endpoint | N=567 | N=566 |
| Primary endpoint | | |
| Mean Annualised Relapse Rate[a] | 0.202 | 0.290 |
| Relative ARR reduction | 30.5% (p=0.0003)* (95%CLs: 15.2%, 43.0%) | |
| Patients with at least one confirmed relapse | 29.3% | 39.4% |
| | | |
| Secondary endpoints | | |
| Confirmed Disability Accumulation (CDA)[b] | N=567 | N=566 |
| Patients[b] with first 12-week CDA | 10.8% | 13.2% |
| Relative risk reduction[c] | 17% (p = 0.2939) (95%CLs: -18%, 42%) | |
| Patients[b] with first 24-week CDA | 8.7% | 10.5% |
| Relative risk reduction[c] | 16% (p = 0.3720) (95%CLs: -24%, 43%) | |
| | | |
| MRI Endpoints | | |
| Cumulative number of Combined Unique Active Lesions (CUALs) | N=539 | N=536 |
| Mean number of CUALs per year[d] | 1.41 | 3.16 |
| Relative reduction | 56% (p<0.0001)* (95% CL: 45.8%, 63.6%) | |

All analyses are based on the full analysis set (FAS), which includes all randomised 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 randomisation [Yes/No]) and the number of relapses in the year prior to study entry(≤1, ≥2) as covariates)

b Based on time to first 12-Week/24-Week CDA event up to EOS (Kaplan-Meier estimates at Week 108)

c 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). Two pre-planned indirect comparison methods both showed a consistent clinically meaningful effect of ponesimod compared to placebo on time to first 12-week CDA, the Matching-Adjusted Indirect Comparison (MAIC) approach showed that ponesimod reduced 12-week CDA by 40% compared to placebo (hazard ratio: 0.60 [95% CI: 0.34, 1.05]) and the Model-Based Meta-Analysis (MBMA) showed that ponesimod reduced the risk of 12-week CDA by 39% compared to placebo (hazard ratio: 0.61 [95% CLs: 0.47, 0.80]).

d 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)

* statistically significant according to the predefined multiplicity testing strategy, CLs: Confidence Limits.

## 5.2 PHARMACOKINETIC PROPERTIES

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.

### Absorption

The time to reach maximum plasma concentration of ponesimod is 2-4 hours post-dose. The absolute oral bioavailability of a 10 mg dose is 83.8%.

#### Food effect

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

### Distribution

Following intravenous administration in healthy subjects, the steady-state volume of distribution of ponesimod is 160 L.

Ponesimod is highly bound to plasma proteins, (> 99%) and is mainly (78.5%) distributed in the plasma fraction of whole blood. Animal studies show that ponesimod readily crosses the blood-brain-barrier.

### Metabolism

Ponesimod is extensively metabolised prior to excretion in humans, though unchanged ponesimod was the main circulating component in plasma. Two inactive circulating metabolites, M12 and M13, have also been identified in human plasma. M13 is approximately 20% and M12 is 6% of total drug-related exposure. Both metabolites are inactive at S1P receptors at concentrations achieved with therapeutic doses of ponesimod.

Experiments with human liver preparations indicate that metabolism of ponesimod to M13 occurs primarily through a combination of non-Cytochrome P450 (CYP450) enzymatic activities. Multiple CYP450 (CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12) and non-CYP450 enzymes catalyze the oxidation of ponesimod to M12. Ponesimod also undergoes direct glucuronidation (mainly UGT1A1 and UGT2B7).

### Elimination

After a single intravenous administration, the total clearance of ponesimod is 3.8 L/hour. 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 faeces (16% as unchanged ponesimod), and 10% to18% in urine (no unchanged ponesimod).

### Specific populations

#### Renal impairment

No dose adjustment is 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 pharmacokinetics 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.

**Hepatic impairment**

In adult subjects with mild, moderate or severe hepatic impairment (Child-Pugh class A, B and C, respectively), no change in ponesimod $C_{max}$ was observed, but ponesimod $AUC_{0-\infty}$ was increased by 1.3- , 2.0- and 3.1- fold respectively compared to healthy subjects.

PONVORY is not recommended in patients with moderate and severe hepatic impairment, as the risk of adverse reactions may be greater.

No dose adjustment is needed in patients with mild hepatic impairment (Child-Pugh class A).

**Age**

The results from population pharmacokinetics of ponesimod demonstrated age (range: 17 to 65 years) was not identified to significantly influence the PK of ponesimod. The population pharmacokinetics results suggest no dose adjustment is necessary in elderly patients.

**Gender**

Gender has no clinically significant influence on ponesimod pharmacokinetics.

**Race**

No clinically relevant pharmacokinetic differences were observed between Japanese and Caucasian subjects.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Ponesimod was negative in a battery of *in vitro* (Ames, chromosomal aberration in mammalian cells) and *in vivo* (micronucleus in rat) assays**.**

### Carcinogenicity

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 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 4 and 19 times the human systemic exposures at MRHD of 20 mg 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 combined total incidence of hemangiosarcoma and hemangioma was increased in all treated males and high dose females. The $AUC_{0-24}$ was approximately 5 times the human systemic exposures at MRHD of 20 mg/day. Similar species-specific incidences of haemangiosarcoma/haemangioma were reported in carcinogenicity studies with drugs of the same pharmacological class. Mechanistic studies showed activation of vascular endothelial cells, leading to induction of abnormal angiogenesis and finally haemangiosarcoma. No sustained vascular endothelial cell activation and no increased incidences of haemangiosarcoma were found in rats.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

### Tablet core

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Colloidal anhydrous silica

Sodium lauryl sulfate

### Tablet coating

**PONVORY 2 mg film-coated tablets**

Opadry II Complete Film Coating System 33G280000 White, ARTG PI No. 140386

**PONVORY 3 mg film-coated tablets**

Opadry II Complete Film Coating System 33G250004 Red, ARTG PI No. 140385

**PONVORY 4 mg film-coated tablets**

Opadry II Complete Film Coating System 33G200005 Purple, ARTG PI No. 140384

**PONVORY 5 mg film-coated tablets**

Opadry II Complete Film Coating System 33G210008 Green, ARTG PI No. 140383

**PONVORY 6 mg film-coated tablets**

Opadry II Complete Film Coating System 33G280000 White, ARTG PI No. 140386

**PONVORY 7 mg film-coated tablets**

Opadry II Complete Film Coating System 33G250004 Red, ARTG PI No. 140385

**PONVORY 8 mg film-coated tablets**

Opadry II Complete Film Coating System 33G200005 Purple, ARTG PI No. 140384

**PONVORY 9 mg film-coated tablets**

Opadry II Complete Film Coating System 33G265005 Brown, ARTG PI No. 140382

**PONVORY 10 mg film-coated tablets**

Opadry II Complete Film Coating System 33G230009 Orange, ARTG PI No. 140381

**PONVORY 20 mg film-coated tablets**

Opadry II Complete Film Coating System 33G220020 Yellow, ARTG PI No. 140387

## 6.2 INCOMPATIBILITIES

Not applicable

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not remove the tablets from the blister until use.

## 6.5 NATURE AND CONTENTS OF CONTAINER

The Alu/alu blister with desiccant consists of a laminated Alu cold form film with integrated desiccant and a laminated Alu push-through lidding film. The blister packs are enclosed within a wallet which has an outer wallet, and a inner wallet which can be pulled out and unfolded. The tablets are presented in a calendar blister.

### Treatment initiation pack

Each blister pack of 14 film-coated tablets for a 2-week treatment schedule contains:

2 film-coated tablets of 2 mg

2 film-coated tablets of 3 mg

2 film-coated tablets of 4 mg

1 film-coated tablet of 5 mg

1 film-coated tablet of 6 mg

1 film-coated tablet of 7 mg

1 film-coated tablet of 8 mg

1 film-coated tablet of 9 mg

3 film-coated tablets of 10 mg

### PONVORY 20 mg film-coated tablets (maintenance pack)

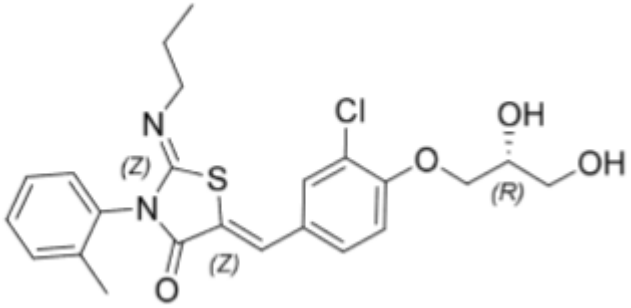
Pack of 28 film-coated tablets for a 4-week treatment schedule.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure:




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

Molecular Mass: 460.97 g/mol

### CAS number:

854107-55-4

## 7 MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

## 8 SPONSOR

JANSSEN-CILAG Pty Ltd
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Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

## 9 DATE OF FIRST APPROVAL

11 March 2022