PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

PONVORY 2 mg film-coated tablets

PONVORY 3 mg film-coated tablets

PONVORY 4 mg film-coated tablets

PONVORY 5 mg film-coated tablets

PONVORY 6 mg film-coated tablets

PONVORY 7 mg film-coated tablets

PONVORY 8 mg film-coated tablets

PONVORY 9 mg film-coated tablets

PONVORY 10 mg film-coated tablets

PONVORY 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PONVORY 2 mg film-coated tablets

Each film-coated tablet contains 2 mg of ponesimod

Excipient with known effect

Each tablet contains 23 mg of lactose.

PONVORY 3 mg film-coated tablets

Each film-coated tablet contains 3 mg of ponesimod

Excipient with known effect

Each tablet contains 22 mg of lactose

PONVORY 4 mg film-coated tablets

Each film-coated tablet contains 4 mg of ponesimod

Excipient with known effect

Each tablet contains 21 mg of lactose.

PONVORY 5 mg film-coated tablets

Each film-coated tablet contains 5 mg of ponesimod

Excipient with known effect

Each tablet contains 118 mg of lactose

PONVORY 6 mg film-coated tablets

Each film-coated tablet contains 6 mg of ponesimod

Excipient with known effect

Each tablet contains 117 mg of lactose

PONVORY 7 mg film-coated tablets

Each film-coated tablet contains 7 mg of ponesimod

Excipient with known effect

Each tablet contains 117 mg of lactose.

PONVORY 8 mg film-coated tablets

Each film-coated tablet contains 8 mg of ponesimod

Excipient with known effect

Each tablet contains 116 mg of lactose.

PONVORY 9 mg film-coated tablets

Each film-coated tablet contains 9 mg of ponesimod

Excipient with known effect

Each tablet contains 115 mg of lactose.

PONVORY 10 mg film-coated tablets

Each film-coated tablet contains 10 mg of ponesimod

Excipient with known effect

Each tablet contains 114 mg of lactose.

PONVORY 20 mg film-coated tablets

Each film-coated tablet contains 20 mg of ponesimod

Excipient with known effect

Each tablet contains 104 mg of lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

PONVORY 2 mg film-coated tablets

White, round, biconvex, film-coated tablet of 5 mm diameter with “2” on one side and an arch on the other side.

PONVORY 3 mg film-coated tablets

Red, round, biconvex, film-coated tablet of 5 mm diameter with “3” on one side and an arch on the other side.

PONVORY 4 mg film-coated tablets

Purple, round, biconvex, film-coated tablet of 5 mm diameter with “4” on one side and an arch on the other side.

PONVORY 5 mg film-coated tablets

Green, round, biconvex, film-coated tablet of 8,6 mm diameter with “5” on one side and an arch and an “A” on the other side.

PONVORY 6 mg film-coated tablets

White, round, biconvex, film-coated tablet of 8,6 mm diameter with “6” on one side and an arch and an “A” on the other side.

PONVORY 7 mg film-coated tablets

Red, round, biconvex, film-coated tablet of 8,6 mm diameter with “7” on one side and an arch and an “A” on the other side.

PONVORY 8 mg film-coated tablets

Purple, round, biconvex, film-coated tablet of 8,6 mm diameter with “8” on one side and an arch and an “A” on the other side.

PONVORY 9 mg film-coated tablets

Brown, round, biconvex, film-coated tablet of 8,6 mm diameter with “9” on one side and an arch and an “A” on the other side.

PONVORY 10 mg film-coated tablets

Orange, round, biconvex, film-coated tablet of 8,6 mm diameter with “10” on one side and an arch and an “A” on the other side.

PONVORY 20 mg film-coated tablets

Yellow, round, biconvex, film-coated tablet of 8,6 mm diameter with “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) defined by clinical or imaging features.

4.2 Posology and method of administration

Posology

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 - Infections).

Liver function tests

Review results of serum transaminase enzymes and bilirubin levels obtained within the last 6 months (see section 4.4 - Liver Injury).

Pregnancy test

Before initiation of treatment in women of childbearing potential, a recent negative pregnancy test result must be available (see section 4.6 - Contraception).

Ophthalmic evaluation

Obtain an expert evaluation of the fundus, including the macula (see section 4.4 - Macular Oedema).

Cardiac evaluation

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 essential (see section 4.2 - First Dose Monitoring in Patients with Certain Preexisting Cardiac Conditions and section 4.4 – Brady-dysrhythmia and Atrioventricular Conduction Delays).

Determine whether patients are taking other medicines that could slow heart rate or atrioventricular (AV) conduction (see section 4.5 – Anti-Dysrhythmic Medicines, QT Prolonging Medicines, Medicines That May Decrease Heart Rate and Beta-Blockers).

Current or prior medications

If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these medicines, consider possible unintended additive immunosuppressive effects before initiating treatment with PONVORY (see section 4.4 - Infections and Interactions - Anti Neoplastic, Immunosuppressive, or Immune-Modulating Therapies).

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating PONVORY; VZV vaccination of antibody-negative patients is essential prior to commencing treatment with PONVORY (see section 4.4 - Infections).

Recommended dosage

Treatment initiation

The starter pack must be used for patients initiating treatment with PONVORY (see section 6.5). Initiate PONVORY treatment with a 14-day up-titration; start with one 2 mg tablet orally once daily and progress with the titration schedule outlined in Table 1 (see section 4.4 -Bradydysrhythmia and Atrioventricular Conduction Delays).

Table 1: 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 – Missed Doses).

Maintenance dosage

After dose titration is complete (see section 4.2 - Treatment Initiation), the recommended maintenance dosage of PONVORY is one 20 mg tablet taken orally once daily.

First dose monitoring in patients with certain preexisting 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 – Bradydysrhythmia and Atrioventricular Conduction Delays and section 5.1).

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 yet occurred.
- The ECG 4 hours post dose shows new onset second-degree or higher AV block.

If post-dose symptomatic bradycardia, brady-dysrhythmia, 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.

Note: If at any time during initiation of PONVORY treatment, the findings or symptoms are considered clinically significant, PONVORY treatment should be stopped.

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 preexisting heart and cerebrovascular conditions (see section 4.4 – Bradydysrhythmia 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 medicines with a known risk of torsades de pointes (see section 4.4 - Bradydysrhythmia and Atrioventricular Conduction Delays and Interactions - Anti-Dysrhythmic Medicines, QT Prolonging Medicines, Medicines That May Decrease Heart Rate).
- Receiving concurrent therapy with medicines that slow heart rate or AV conduction (see section 4.5 - Anti- Dysrhythmic Medicines, QT Prolonging Medicines, Medicines 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 starter 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 - First Dose Monitoring in Patients with Certain Preexisting Cardiac Conditions).

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 PONVORY 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 - 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 - Special populations, Renal impairment).

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) (see section 5.2 - Special populations, Hepatic impairment).
Based on clinical pharmacology studies in adult subjects with moderate or severe hepatic impairment, ponesimod $AUC_{(0\text{-inf})}$ was increased 2,0- and 3,1-fold respectively, compared to healthy subjects. PONVORY is contraindicated 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 5.2 - Special populations, Hepatic impairment).

Method Administration

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

4.3 Contraindications

PONVORY is contraindicated:

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- Immunodeficient states (see section 4.4).
- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation, or New York Heart Association (NYHA) Class III or IV heart failure.
- Patients who have presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, or sick sinus syndrome, unless patient has a functioning pacemaker (see section 4.4).
- Severe active infections, active chronic infections.
- Active malignancies.
- Moderate or severe hepatic impairment. (Child-Pugh class B and C, respectively).
- During pregnancy and in women of childbearing potential not using highly effective contraception (see section 4.6).

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 S1P receptor modulators.

In the Phase 3 OPTIMUM study the overall rate of infections was 54,2 %. Nasopharyngitis and viral infections have been reported in PONVORY-treated patients. Serious or severe infections occurred in 1,6 % in PONVORY-treated patients.

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. Absolute lymphocyte counts of < 0,2 x 10^9/L if confirmed, should lead to interruption of PONVORY therapy until the levels reach ≥ 0,8 x 10^9/L when re-initiation of PONVORY can be considered.

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 - 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.

In the OPTIMUM study, the rate of herpetic infections was 4,8 % in PONVORY treated patients. In 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. Medical practitioners 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 an S1P-receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Medical practitioners 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/or concomitant treatment with anti-neoplastic, immune modulating, or immunosuppressive therapies

In patients that are taking anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) or if there is a history of prior use of these medicines, possible unintended additive immune system effects should be considered before initiating treatment with PONVORY (see section 4.5)

When switching from medicines with prolonged immune effects, the half-life and mode of action of these medicines must be considered in order to avoid unintended additive effects on the immune system while at the same time minimising risk of disease reactivation, when initiating PONVORY.

Pharmacokinetic/pharmacodynamic modeling indicates lymphocyte counts returned to the normal range in >90% of healthy subjects within 1 week of stopping PONVORY therapy (see section 5.1). 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 addictive effect on the immune system, and therefore caution should be applied up to 1 week after the last dose of PONVORY (see section 4.5).

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 and 4 weeks after a planned vaccination (see section 4.5 - 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 PONVORY, the rate of macular oedema was 0,7 %. Most cases occurred within the first 6 months of therapy.

In the OPTIMUM study, macular oedema was reported in 1,1 % of PONVORY treated patients.

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 and have follow-up evaluations while receiving therapy.

Bradydysrhythmia 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 - Recommended Dosage, section 5.1 - 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 dysrhythmia, 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.

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. 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.

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. No second-degree AV blocks, Mobitz type I (Wenckebach), were observed in OPTIMUM study. The conduction abnormalities were transient, asymptomatic, resolved within 24 hours, resolved without intervention, and did not require discontinuation of PONVORY treatment.

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 dysrhythmias treated with Class Ia or Class III anti-arrhythmic medicines (see section 4.5 - Anti- Dysrhythmic Medicines, QT Prolonging medicines, Medicines 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).

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 section 4.2 - Recommended Dosage).
- 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 - Assessments Prior to First Dose of PONVORY, First Dose Monitoring in Patients with Certain Preexisting 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 to determine if treatment can be initiated and 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 medicines that decrease heart rate (e.g., beta blockers, non-dihydropyridine calcium channel blockers - diltiazem and verapamil, and other medicines that may decrease heart rate such as digoxin). Concomitant use of these medicines 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 strategy or if treatment can be initiated.
- 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 - Beta-Blockers).
- For patients taking other medicines that decrease heart rate, treatment with PONVORY should not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate (see section 4.2 - First Dose Monitoring in Patients with Certain Preexisting Cardiac Conditions and Interactions, Anti-Dysrhythmic medicines, QT Prolonging Medicines, Medicines 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 treatment with Day 1 of the dose titration (new starter pack) and follow titration monitoring recommendations (see section 4.2 - Missed Dose).

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_1at 2 years was 8,3 % in PONVORY treated patients. 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 serum 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.

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, ALT increased eight times ULN in 0,7 % PONVORY-treated patients. 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 liver injury is confirmed.

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 section 4.2).

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

Foetal risk

Based on animal studies, PONVORY may cause foetal harm. Due to the risk to the foetus, PONVORY is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraception (see section 4.3 and section 4.6). 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

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an 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 medical practitioner should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral hemorrhage. 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 immunosuppressive or immune-modulating therapies

When switching from medicines with prolonged immune effects, the half-life and mode of action of these medicines must be considered in order to avoid unintended additive effects on the immune system while at the same time minimising risk of disease reactivation, when initiating PONVORY.

Severe exacerbation of disease after stopping PONVORY

Severe exacerbation of disease, including disease rebound, has been reported after discontinuation of an 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 - 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.

Intolerance to excipients

Lactose

PONVORY contains lactose. Patients with rare hereditary problems of galactose intolerance; e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption should not take PONVORY

Sodium

This medicine also contains more than 1 mmol (or 27,2 mg) sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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 - Infection).

When switching from medicines with prolonged immune effects, the half-life and mode of action of these medicines must be considered in order to avoid unintended additive effects on the immune system (see section 4.4 - Unintended Additive Immunosuppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Therapies).

Anti- Dysrhythmic medicines, QT prolonging medicines, medicines that may decrease heart rate

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

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol). Anti-Dysrhythmic medicines 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 not be initiated in patients who are concurrently treated with QT prolonging medicines with known dysrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other medicines that may decrease heart rate (e.g., digoxin) (see section 4.4 - Bradydysrhythmia and Atrioventricular Conduction Delays and 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, if treatment is initiated.

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 – Bradydysrhythmia and Atrioventricular Conduction Delays). Beta blocker treatment can be initiated in patients receiving stable doses of PONVORY.

In a medicine-medicine interaction study, the up-titration regimen of PONVORY (see section 4.2 – Recommended Dosage) 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 PONVORY alone, the combination with propranolol after the first dose of PONVORY (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 PONVORY (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 - 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 - Infection).

Effect of other drugs on PONVORY

In vitro studies with human liver preparations indicate that metabolism of PONVORY 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.

Medicines that are inhibitors of major CYP or UGT enzymes are unlikely to impact the pharmacokinetics of PONVORY.

Co administration of PONVORY with strong CYP3A4 and UGT1A1 inducers may decrease the systemic exposure of PONVORY. It is unclear whether this decrease in PONVORY systemic exposure would be considered of clinical relevance.

PONVORY is not a substrate of P-gp, BCRP, OATP1B1 or OATP1B3 transporters. Medicines that are inhibitors of these transporters are unlikely to impact the PK of PONVORY.

Effect of PONVORY on other medicines

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

Oral contraceptives

Co-administration of PONVORY, with an oral hormonal contraceptive (containing 1 mg norethisterone/norethindrone and 35 µg ethinyl estradiol) showed no clinically relevant pharmacokinetic interaction with PONVORY. Therefore, concomitant use of PONVORY 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 PONVORY on their exposure is not expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

PONVORY is contraindicated during pregnancy (see section 4.3). 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 embryofoetal harm when administered to a pregnant woman (see section 5.3). Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod- induced developmental toxicity, including embryo lethality and an increase in foetal malformations (skeletal and visceral). The $AUC_{0\text{-}24}$ 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.

Contraception

Females

PONVORY is contraindicated in women of childbearing potential not using highly effective contraception (see section 4.3). Before initiation of PONVORY treatment in women of childbearing potential, a recent negative pregnancy test result must be available, and women should be counseled on the potential for a serious risk to the foetus and the need for highly effective contraception during treatment with PONVORY (see section 4.6 - Pregnancy). Since it takes approximately 1 week to eliminate the compound from the body after stopping treatment, the potential risk to the foetus may persist and women must use highly effective contraception during this period (see section 4.4 - Foetal Risk).

Breastfeeding

PONVORY should not be used during breastfeeding. It is unknown whether ponesimod or its metabolites are excreted in human milk. A study in lactating rats has shown excretion of ponesimod in milk (see section 5.3).

A risk to newborns/infants cannot be excluded.

4.7 Effects on ability to drive and use machines

PONVORY may cause dizziness and somnolence. Patients should establish how PONVORY affects them before they drive or use machines.

4.8 Undesirable effects

A total of 1 438 MS patients have received PONVORY at doses of at least 2 mg daily. These patients were included in the OPTIMUM study and in a Phase 2 (6-month placebo controlled) study in patients with MS and their uncontrolled extension studies.

In the OPTIMUM study, 83.1 % of PONVORY treated patients completed 2 years of study treatment. Adverse events led to discontinuation of treatment in 8,7 % of PONVORY treated patients. The most common adverse reactions (incidence at least 10 %) in PONVORY treated patients in the OPTIMUM study were alanine

aminotransferase increases (19,5 %), nasopharyngitis (19,3 %) and upper respiratory tract infection (10,6 %).

Summary of the safety profile

Table 2 represents the adverse reactions reported with PONVORY in controlled clinical trials and uncontrolled extension trials, ranked by frequency, with the most frequent reactions first within each MedDRA System Organ Class. Frequencies were defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); and uncommon (≥ 1/1000 to < 1/100).

Table 2: Adverse Reactions Reported with PONVORY in Controlled Clinical Trials and Uncontrolled Extension Trials.

MedDRA System Organ Class (SOC)	**Very Common**	**Common**	**Uncommon**
Infections and infestations	Nasopharyngitis, Upper respiratory tract infection	Urinary tract infection, Bronchitis, Influenza, Rhinitis, Respiratory tract infection, Respiratory tract infection viral, Pharyngitis, Sinusitis, Viral Infection, Herpes zoster, Laryngitis, Pneumonia	
Blood and lymphatic system disorders		Lymphopenia, Lymphocyte count decreased	
Psychiatric disorders		Depression, Insomnia, Anxiety	
Nervous system disorders		Dizziness, Hypoesthesia, Somnolence, Migraine	
Eye disorders		Macular oedema	
Ear and labyrinth		Vertigo	

disorders			
Cardiac disorders			Bradycardia
Vascular disorders		Hypertension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Cough	
Gastrointestinal disorders		Dyspepsia	Dry mouth
Musculoskeletal and connective tissue disorders		Back pain, Arthralgia, Pain in extremity, Ligament sprain	Joint swelling
General disorders and administration site conditions		Fatigue, Pyrexia, Peripheral oedema, Chest discomfort	
Investigations	Alanine Aminotransferase increased	Increased Aspartate aminotransferase, Hypercholesterolaemia, Increased hepatic enzyme, Increased C-reactive protein, Increased transaminases, Increased blood cholesterol	Hyperkalaemia

Seizures

In the OPTIMUM study, cases of seizures were reported in 1,4 % of PONVORY treated patients. 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 - Respiratory Effects).

Malignancies

In the OPTIMUM study, a case of malignant melanoma and two cases of basal cell carcinoma (0,4 %) were reported in PONVORY treated patients. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator. Medical practitioners 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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za/Publications/Index/8**

4.9 Overdose

Signs and symptoms

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 must include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed (see section 4.4 - Bradydysrhythmia and Atrioventricular Conduction Delays, Increased Blood Pressure and section 5.1 - Heart Rate and Rhythm).

Treatment

There is no specific antidote to PONVORY. Neither dialysis nor plasma exchange would result in meaningful removal of PONVORY 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 centre to obtain the latest recommendations for the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.32.16 Other

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 located on 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, PONVORY 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.

Pharmacokinetic/Pharmacodynamic modelling 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.
In the OPTIMUM study, lymphocyte counts returned to the normal range in 94 % of patients and to above 0.8 x 10^9 cells/L in 99 % of patients at the first scheduled follow-up visit (day 15) upon discontinuation of PONVORY treatment.

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 - Bradydysrhythmia and Atrioventricular Conduction Delays). The heart rate decreases plateaued at doses greater than or equal to 40 mg, and Bradydysrhythmic 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 PONVORY 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 – 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) PONVORY at steady-state, PONVORY 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 PONVORY 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 PONVORY treated subjects and were greater than in subjects taking

placebo (see section 4.4 - Respiratory Effects). These effects can be reversed with administration of a short acting beta2 agonist.

5.2 Pharmacokinetic properties

Following ponesimod oral dosing, Cmax 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 characterised 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 IV 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.

Biotransformation

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 catalyse the oxidation of ponesimod to M12. Ponesimod also undergoes direct glucuronidation (mainly UGT1A1 and UGT2B7).

Elimination

After a single IV 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 14C ponesimod, 57 % to 80 % of the dose was recovered in faeces (16 % as unchanged ponesimod), and 10 % to 18 % in urine (no unchanged ponesimod).

Linearity

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 4 days of administration of the maintenance dose of ponesimod.

Special 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 (Cr_{Cl}) 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 (Cr_{Cl} > 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.

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

$AUC_{(0\text{-}inf)}$ 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

Repeat-dose toxicity

In the lung, transient adaptive pulmonary histiocytosis and lung weight increase were observed in mice, rats, and dogs after subacute treatment with ponesimod, but

were no longer present or were less pronounced after prolonged treatment. 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 C_{max} and AUC_{0-24} 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, secondary to haemodynamic changes, after 13, 26, and 52 weeks of treatment at ≥ 5 mg/kg/day. The dog is known to be particularly sensitive to haemodynamic changes in the heart and the associated toxicity. 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 Mutagenicity

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 3,6 and 18,7 times the human systemic exposures at RHD 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 haemangiosarcoma and haemangioma was increased in all

treated males and high dose level females. The lowest dose tested in females is the no-observed-effect-level (NOEL) for carcinogenesis, and the AUC_{0-24} is 2,4 times the human systemic exposures at RHD of 20 mg.

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

Reproductive Toxicology

When ponesimod was orally administered (1, 10, 40 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-foetal 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 foetal developmental toxicity in rats was established at 1 mg/kg/day. When ponesimod was orally administered (0,25, 1, 4 mg/kg/day) to pregnant rabbits during the period of organogenesis, a slight increase in post-implantation losses and foetal findings (visceral and skeletal) were noted at 4 mg/kg/day. The embryo-foetal 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, or 20 mg/kg) 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. 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.

Ponesimod was present in the plasma of F1 pups, indicating exposure from the milk of the lactating dam.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone K30

Silica colloidal anhydrous

Sodium laurylsulfate

Tablet coating

Hypromellose/Hydroxypropyl methylcellulose 2910

Lactose monohydrate

Macrogol/Polyethylene glycol 3350

Titanium dioxide

Triacetin

Iron oxide red (E172) included in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg and 10 mg film-coated tablets.

Ferrosoferric oxide/Black iron oxide (E172) included in 4 mg, 5 mg, 8 mg and 9 mg film-coated tablets

Iron oxide yellow (E172) included in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg and 20 mg film-coated tablets

Opadry® II is used for the coating of the tablets.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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.

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.

6.6 Special precautions for disposal and other handling

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand 1685, South Africa

Tel: +27 (11) 518 7000

8. REGISTRATION NUMBERS

PONVORY 2 mg film-coated tablets:	56/32.16/0592
PONVORY 3 mg film-coated tablets:	56/32.16/0593
PONVORY 4 mg film-coated tablets:	56/32.16/0594
PONVORY 5 mg film-coated tablets:	56/32.16/0595
PONVORY 6 mg film-coated tablets:	56/32.16/0596
PONVORY 7 mg film-coated tablets:	56/32.16/0597
PONVORY 8 mg film-coated tablets:	56/32.16/0598
PONVORY 9 mg film-coated tablets:	56/32.16/0599
PONVORY 10 mg film-coated tablets:	56/32.16/0600
PONVORY 20 mg film-coated tablets:	56/32.16/0601

9. DATE OF FIRST AUTHORISATION

19 September 2023

10. DATE OF REVISION OF THE TEXT

N/A