ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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 (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) with active disease defined by clinical or imaging features.

4.2 Posology and method of administration

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

Posology

Treatment initiation
Treatment must be started with the 14-day treatment initiation pack (see section 6.5). Treatment starts with one 2 mg tablet orally once daily on day 1 and dose-escalation progresses with the titration schedule outlined in Table 1.

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 also section 4.2, "Re-initiation of therapy following treatment interruption during dose titration or maintenance period").

Maintenance dose
After dose titration is complete (see also section 4.2, Treatment initiation), the recommended maintenance dose of Ponvory is one 20 mg tablet taken orally once daily.

Re-initiation of therapy following treatment interruption during dose titration or maintenance period
- 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 (2 mg) of the titration regimen (new treatment initiation pack).

The same first dose monitoring as for treatment initiation is recommended when 4 or more consecutive doses of ponesimod are missed during the titration or maintenance periods.

Special populations

Elderly population
Clinical studies of ponesimod did not include patients aged 65 years and older. Ponesimod should be prescribed with caution in patients aged 65 years and over due to the lack of data on safety and efficacy.

Renal impairment
Based on clinical pharmacology studies, no dose adjustment is needed in patients with mild to severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) (see section 5.2).

Ponvory is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively) (see sections 4.3, 5.2).

Paediatric population
The safety and efficacy of Ponvory in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Ponesimod should be administered orally once daily. Ponesimod can be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Immunodeficient state (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 effective contraception (see section 4.6).

4.4 Special warnings and precautions for use

Bradyarrhythmia

Initiation of treatment with ponesimod
Prior to treatment initiation with ponesimod, an electrocardiogram (ECG) in all patients should be obtained to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, first-dose monitoring is recommended (see below).

Initiation of ponesimod treatment may result in a transient decrease in heart rate (HR) and AV conduction delays (see sections 4.8 and 5.1), therefore an up-titration scheme must be used to reach the maintenance dose of ponesimod (20 mg) (see section 4.2).

After the first dose of ponesimod, the decrease in HR typically begins within an hour and reaches its nadir within 2-4 hours. The HR typically recovers to baseline levels 4-5 hours after administration. The mean decrease in HR on day 1 of dosing (2 mg) was 6 bpm. With up-titration after day 1, the decrease in HR is less pronounced with no further post-dose decrease in HR observed after day 3.

Caution should be applied when ponesimod 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 ponesimod (see section below and section 4.5).

For patients receiving a stable dose of a beta-blocker, the resting HR should be considered before introducing ponesimod treatment. If the resting HR is greater than 55 bpm under chronic beta-blocker treatment, ponesimod can be introduced. If resting HR is less than or equal to 55 bpm, beta-blocker treatment should be interrupted until the baseline HR is greater than 55 bpm. Treatment with ponesimod can then be initiated and treatment with a beta-blocker can be reinitiated after ponesimod has been up-titrated to the target maintenance dose (see section 4.5). Beta-blocker treatment can be initiated in patients receiving stable doses of ponesimod.

First dose monitoring in patients with certain pre-existing cardiac conditions
Because initiation of ponesimod treatment may result in a decrease in 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 5.1).

Administer the first dose of ponesimod 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-hours is recommended if any of the following abnormalities are present (even in the absence of symptoms), continue monitoring until the abnormality resolves:
- HR 4 hours postdose is less than 45 bpm
- HR 4 hours postdose is at the lowest value postdose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 4 hours postdose shows new onset second-degree or higher AV block

If postdose 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.

Cardiologist advice should be obtained before initiation of ponesimod in the following patients to determine overall benefit risk and the most appropriate monitoring strategy
- In patients with significant QT prolongation (QTc greater than 500 msec) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes)
- In patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) anti-arrhythmic medicinal products (see section 4.5)
- 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, since significant bradycardia may be poorly tolerated in these patients, treatment is not recommended
- 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)
- In patients with a history of recurrent syncope or symptomatic bradycardia
- 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 HR such as digoxin) (see above and section 4.5), consider potential need to switch to non-HR lowering medicinal products. Concomitant use of these medicinal products during ponesimod initiation may be associated with severe bradycardia and heart block.

<u>Infections</u>

Risk of infections
Ponesimod causes a dose-dependent reduction in peripheral lymphocyte count to 30-40% of baseline values due to reversible sequestration of lymphocytes in lymphoid tissues. Ponesimod may therefore increase the risk of infections (see section 4.8). Life-threatening and rare fatal infections have been reported in association with sphingosine 1-phosphate (S1P) receptor modulators.

Before initiating treatment with ponesimod, results from a recent complete blood count (CBC) with differential (including lymphocyte count) (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed. Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/L, if confirmed, should lead to interruption of ponesimod therapy until the level reaches $>0.8 \times 10^9$/L when re-initiation of ponesimod can be considered.

Initiation of treatment with ponesimod should be delayed in patients with severe active infection until resolution.

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

In the development program, pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, were restored to normal within 1 week after discontinuation of ponesimod. In the OPTIMUM study, peripheral lymphocyte counts were restored to normal within 2 weeks after discontinuation of ponesimod, which was the first timepoint evaluated. Vigilance for signs and symptoms of infection should be continued for 1-2 weeks after ponesimod is discontinued (see below and section 4.8).

Herpes viral infections
Cases of herpes viral infection have been reported in the development program of ponesimod (see section 4.8).

Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ponesimod. The treatment with ponesimod should be delayed for 4 weeks after vaccination to allow the full effect of vaccination to occur. See Vaccinations section 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 ponesimod-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. Ponesimod 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 or PML-IRIS (Immune reconstitution inflammatory syndrome) have been reported in ponesimod-treated patients in the development program; however, PML or PML-IRIS have been reported in patients treated with S1P receptor modulators and other multiple sclerosis (MS) therapies and have 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 ponesimod should be suspended until PML has been excluded. If confirmed, treatment with ponesimod should be discontinued.

IRIS has been reported in patients treated with S1P receptor modulators who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient’s condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within four months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Prior and 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 medicinal products, possible unintended additive immune system effects should be considered before initiating treatment with ponesimod (see section 4.5).

When switching from medicinal products with prolonged immune effects, the half-life and mode of action of these medicinal products 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 ponesimod.

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

Vaccinations
No clinical data are available on the efficacy and safety of vaccinations in patients taking ponesimod. Vaccinations may be less effective if administered during ponesimod treatment.

Avoid the use of live attenuated vaccines while patients are taking ponesimod. If the use of live attenuated vaccine immunisation is required, ponesimod treatment should be paused from 1 week prior to 4 weeks after a planned vaccination (see section 4.5).

Macular oedema

Ponesimod increases the risk of macular oedema (see section 4.8). 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 ponesimod therapy.

In the clinical trial experience in patients with all doses of ponesimod, the rate of macular oedema was 0.7%, the majority of patients had pre-existing risk factors or comorbid conditions. Most cases occurred within the first 6 months of therapy.

Ponesimod therapy should not be initiated in patients with macular oedema until resolution.

Continuation of ponesimod therapy in patients with macular oedema has not been evaluated. Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ponesimod should be discontinued. A decision on whether ponesimod should be re-initiated after resolution needs to 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 examinations of the fundus, including the macula, prior to treatment initiation with ponesimod and have follow-up evaluations while receiving therapy.

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 ponesimod-treated patients mostly occurring in the first month after treatment initiation (see section 4.8). Respiratory symptoms

associated with ponesimod treatment can be reversed with administration of a short-acting $beta_2$ agonist.

Ponesimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Spirometry evaluation of respiratory function should be performed during therapy with ponesimod if clinically indicated.

Liver injury

Elevations of transaminases may occur in ponesimod-treated patients (see section 4.8). Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of ponesimod therapy.

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. Ponesimod should be discontinued if significant liver injury is confirmed (for example, ALT exceeds 3 -fold ULN and total bilirubin exceeds 2 -fold ULN).

Although there are no data to establish that patients with pre-existing liver disease are at increased risk to develop elevated liver function test values when taking ponesimod, caution should be exercised when using ponesimod in patients with a history of significant liver disease (see section 4.2).

Increased blood pressure

A mild reversible increase in blood pressure (mean change less than 3 mmHg) was observed in patients treated with ponesimod (see section 4.8). Blood pressure should be regularly monitored during treatment with ponesimod and managed appropriately.

Cutaneous neoplasm

As there is a potential risk of skin malignancies (see section 4.8), 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.

Women of childbearing potential

Based on animal studies, ponesimod may cause foetal harm. Due to the risk to the foetus, ponesimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception (see sections 4.3 and 4.6). Before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available (see section 4.6). Because it takes approximately 1 week to eliminate ponesimod from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 1 week after stopping ponesimod treatment.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. Such events have not been reported for ponesimod-treated patients in the development program. However, should a ponesimod-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, ponesimod should be discontinued.

Return of disease activity after ponesimod discontinuation

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 ponesimod treatment. Patients should be observed for a severe exacerbation or return of high disease activity upon ponesimod discontinuation and appropriate treatment should be instituted, as required (see above).

After stopping Ponvory in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS) (see above).

Excipients

Lactose
Ponvory contains lactose (see section 2). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immune-modulating, or immunosuppressive therapies

Ponesimod 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).

Anti-arrhythmic medicinal products, QT prolonging medicinal products, medicinal products that may decrease heart rate

Ponesimod has not been studied in patients taking QT prolonging medicinal products (see section 4.4).

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.

In a drug-drug interaction study, the up-titration regimen of ponesimod (see section 4.2) was administered to subjects receiving propranolol (80 mg) once daily at steady-state. 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. No significant changes in pharmacokinetics of ponesimod or propranolol were observed.

Vaccines

Vaccinations may be less effective if administered while being treated with ponesimod and up to 1 week after its discontinuation (see section 4.4).

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ponesimod treatment and up to 1 week after its discontinuation of treatment with ponesimod (see section 4.4).

Effect of other medicinal products on ponesimod

Medicinal products that are inhibitors of major CYP or UGT enzymes are unlikely to impact the pharmacokinetics of ponesimod (see section 5.2).

No dose adjustment is needed when ponesimod is co-administered with strong CYP3A4 and UGT1A1 inducers. Co-administration of carbamazepine 300 mg twice daily (a strong CYP3A4 and UGT1A1 inducer) at steady-state decreased ponesimod C_{max} by 19.6% and AUC by 25.7%. This decrease is not clinically relevant.

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

Effect of ponesimod on other medicinal products

Ponesimod and its metabolites are unlikely to show any clinically relevant drug-drug interaction potential for CYP or UGT enzymes, or transporters (see section 5.2).

Oral contraceptives

Co-administration of ponesimod, with an oral hormonal contraceptive (containing 1 mg norethisterone/norethindrone and 35 mcg 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Ponvory is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). 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 foetus and the need for effective contraception during treatment with ponesimod. Since it takes approximately 1 week to eliminate ponesimod from the body after stopping treatment, the potential risk to the foetus may persist and women must use effective contraception during this period (see section 4.4).

Specific measures are also included in the Healthcare Professional checklist. These measures must be implemented before ponesimod is prescribed to female patients and during treatment.

When stopping ponesimod therapy for planning a pregnancy the possible return of disease activity should be considered (see section 4.4).

Pregnancy

Ponvory is contraindicated during pregnancy (see section 4.3). Although there are no data from the use of ponesimod in pregnant women, studies in animals have shown reproductive toxicity (see section 5.3). If a woman becomes pregnant during treatment, ponesimod must be immediately discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment (see section 5.3) and follow-up examinations should be performed.

Based on clinical experience in patients receiving another S1P receptor modulator, the use is associated with an increased risk of major congenital malformations.

Breast-feeding

It is unknown whether ponesimod or its metabolites are excreted in human milk. A study in lactating rats has indicated excretion of ponesimod in milk (see section 5.3). A risk to newborns/infants cannot be excluded. Ponvory should not be used during breast-feeding.

Fertility

The effect of ponesimod on human fertility has not been evaluated. Data from preclinical studies do not suggest that ponesimod would be associated with an increased risk of reduced fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions are nasopharyngitis (19.7%), alanine aminotransferase increased (17.9%) and upper respiratory tract infection (11%).

Tabulated list of adverse reactions

Adverse reactions reported with ponesimod in controlled clinical trials and uncontrolled extension trials are ranked by frequency, with the most frequent reactions first. Frequencies were defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions

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, hypoaesthesia, somnolence, migraine, seizure	
Eye disorders		macular oedema	
Ear and labyrinth disorders		vertigo	
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, oedema peripheral, chest discomfort	
Investigations	alanine aminotransferase increased	aspartate aminotransferase increased, hypercholesterolaemia, hepatic enzyme increased, C-reactive protein increased, transaminases increased, blood cholesterol increased	hyperkalaemia

Description of selected adverse reactions

Bradyarrhythmia
In the Phase 3 OPTIMUM study (see section 5.1), bradycardia at treatment initiation (sinus bradycardia/HR less than 50 bpm on ECG on day 1) occurred in 5.8% of ponesimod-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 ponesimod treatment. On day 1, 3 patients treated with ponesimod had asymptomatic post-dose HR below or equal to 40 bpm; all 3 patients had baseline HRs below 55 bpm.

Initiation of ponesimod treatment has been associated with transient AV 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 ponesimod -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 ponesimod treatment.

Infections
In the Phase 3 OPTIMUM study (see section 5.1), the overall rate of infections was comparable between the ponesimod-treated patients and those receiving teriflunomide 14 mg (54.2% vs 52.1% respectively). Nasopharyngitis and viral infections were more common in ponesimod-treated patients. Serious or severe infections occurred at a rate of 1.6% in ponesimod-treated patients compared to 0.9% of patients receiving teriflunomide 14 mg.

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

Blood lymphocyte count reduction
In OPTIMUM, 3.2% of ponesimod-treated patients compared to none of the patients receiving teriflunomide 14 mg, experienced lymphocyte counts less than 0.2×10^9/L with values generally resolving to greater than 0.2×10^9/L while remaining on treatment with ponesimod.

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

Liver enzymes elevation
In the OPTIMUM study, ALT increased to three and five times the upper limit of normal (ULN) in 17.3% and 4.6% of ponesimod-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% ponesimod-treated patients compared to 2.1% in patients receiving teriflunomide 14 mg. The majority of elevations occurred within 6 or 12 months of starting treatment. ALT levels returned to normal after discontinuation of ponesimod. Most cases of ALT increases ≥3×ULN resolved on continued ponesimod treatment, and the remaining cases resolved upon treatment discontinuation. In clinical trials, ponesimod was discontinued if the elevation exceeded a 3 -fold increase and the patient showed symptoms related to hepatic dysfunction.

Respiratory effects
Dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) were observed in patients treated with ponesimod (see section 4.4). In OPTIMUM, a higher proportion of ponesimod-treated patients (19.4%) had a reduction of more than 20% from baseline in percent predicted FEV_1 compared to 10.6% of patients receiving teriflunomide 14 mg. The reduction from baseline in percent predicted FEV_1 at 2 years was 8.3% in ponesimod-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 ponesimod because of pulmonary adverse events (dyspnoea). Ponesimod 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.

Increased blood pressure
In OPTIMUM, ponesimod-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 ponesimod was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. The blood pressure values after ponesimod treatment discontinuation indicate reversibility.

Hypertension was reported as an adverse reaction in 10.1% of ponesimod-treated patients and in 9.0% of patients receiving teriflunomide 14 mg.

Cutaneous neoplasm
In OPTIMUM, a case of malignant melanoma and two cases of basal cell carcinoma (0.4%) were reported in ponesimod-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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

In patients with overdose of ponesimod, 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 sections 4.4, 4.8 and 5.1).

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 ponesimod can be reversed by atropine.

In the event of overdose, ponesimod 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

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AE04

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, ponesimod induces a dose-dependent reduction of the peripheral blood lymphocyte count from a single dose of 5 mg onwards, with the greatest reduction observed 6 hours post-dose, caused by reversible sequestration of lymphocytes in lymphoid tissues. After 7 daily doses

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

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 ponesimod.

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

Heart rate and rhythm
Ponesimod causes a transient dose dependent reduction in HR and AV conduction delays upon treatment initiation (see section 4.4). The HR decreases plateaued at doses greater than or equal to 40 mg, and bradyarrhythmic events (AV blocks) were detected at a higher incidence under ponesimod 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 HR induced by ponesimod can be reversed by atropine.

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 (see section 4.4).

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 4.8).

Clinical efficacy and safety

The efficacy of ponesimod 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 ponesimod or teriflunomide 14 mg, beginning with a 14-day dose titration (see section 4.2). 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 ponesimod (N=567) or teriflunomide 14 mg (N=566); 86.4% of ponesimod-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 ponesimod-treated patients had one or more Gd+ T1 lesions on brain MRI (mean 1.9).

Results are presented in Table 3. Analysis of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of ponesimod on the primary and secondary endpoints was consistent with the overall population.

Table 3: OPTIMUM study efficacy results

	Ponesimod 20 mg	Teriflunomide 14 mg
Clinical endpoint	N=567	N=566
Primary endpoint		
Mean Annualised Relapse Rate[a]	0.202	0.290
Relative rate 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 12-week CDA	10.8%	13.2%
Relative risk reduction[c]	17% (p=0.2939) (95% CLs: -18%, 42%)	
Patients[b] with 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% CLs: 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 end of study (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 end of study (Kaplan-Meier estimates at Week 108)

[c] Defined as time to 12-Week/24-Week CDA from baseline to end of study (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

Long-term data

Patients with RMS who completed the phase 3 OPTIMUM study were eligible to enter the exploratory, open-label extension study OPTIMUM-LT. In total, 877 patients were enrolled (i.e., 77.4% of patients from OPTIMUM; n=439 from ponesimod arm and n=438 from teriflunomide arm). All patients received ponesimod 20 mg once daily for up to 240 weeks. The mean treatment duration was 46.91 months (range: 0.7–71.8 months) and drop-out rate was 25.4%. The mean ARR in the extension period was 0.132 (95% CLs: 0.113, 0.152). At Week 384, the Kaplan Meier estimate of patients with a 24-week CDA in the extension study, continuously treated with ponesimod (P20 mg/P20 mg) since core study randomization, was 21.3% (95% CLs: 17.7, 25.6).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Ponvory in one or more subsets of the paediatric population in the treatment of multiple sclerosis (see 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ponesimod is similar in healthy subjects and subjects with multiple sclerosis. The pharmacokinetic profile of ponesimod showed “low to moderate” inter-subject variability, approximately 6% – 33%, and “low” intra-subject variability, approximately 12% - 20%.

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 ponesimod 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.

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.

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.

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.

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).

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.

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 without MS with mild, moderate or severe hepatic impairment (Child-Pugh class A, B and C, respectively, N=8 for each category), ponesimod $AUC_{0-\infty}$ was increased by 1.3-, 2.0- and 3.1 -fold respectively compared to healthy subjects. Based on the population pharmacokinetic assessment in a larger group of subjects (N=1245), including 55 subjects with MS with mild hepatic impairment (classified based on the National Cancer Institute - Organ Dysfunction Working Group criteria), a 1.1-fold increase of ponesimod $AUC_{0-\infty}$ was estimated, compared to subjects with normal hepatic function.

Ponesimod is contraindicated 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 a population pharmacokinetics analysis indicated that age (range: 17 to 65 years) does not significantly influence the pharmacokinetics of ponesimod. Ponesimod has not been investigated in the elderly population (>65 years).

Gender
Gender has no clinically significant influence on ponesimod pharmacokinetics.

Race
No clinically relevant pharmacokinetic differences were observed between Japanese and Caucasian or Black and White subjects.

5.3 Preclinical safety data

In the lung, transient adaptive pulmonary histiocytosis and lung weight increase were observed in mice, rats, and dogs after 4 weeks of administration of ponesimod but were no longer present or were less pronounced after 13 to 52 weeks of administration. 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 systemic exposures following recommended human dose (RHD) of 20 mg/day.

In the dog, arterial lesions observed in the heart were secondary to haemodynamic changes. The dog is known to be particularly sensitive to haemodynamic changes in the heart and the associated toxicity may be species specific and not predictive of a risk in humans. 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.

Genotoxicity and carcinogenicity

Ponesimod did not reveal a genotoxic potential *in vitro* and *in vivo*.

Oral carcinogenicity studies of ponesimod were conducted in mice and rats for up to 2 years. In rats, no neoplastic lesions were observed up to the highest dose tested, corresponding with a plasma ponesimod exposure (AUC) which is 18.7 times that in humans at the RHD of 20 mg. In mice, ponesimod increased the combined total incidence of hemangiosarcoma and hemangioma in all treated males and high dose 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.

Fertility and reproductive toxicity

Ponesimod had no effect on male and female fertility in rats at plasma exposures (AUC) up to approximately 18 and 31 times (for males and females, respectively) that in humans at the RHD of 20 mg/day.

When ponesimod was orally administered to pregnant rats during the period of organogenesis, embryo-foetal survival, growth, and morphological development were severely compromised. Teratogenic effects with major skeletal and visceral abnormalities were also observed. When ponesimod was orally administered to pregnant rabbits during the period of organogenesis, a slight increase in post-implantation losses and foetal findings (visceral and skeletal) were noted. Plasma exposure (AUC) in rats and rabbits at the NOAEL (1 mg/kg/day in both species) is less than that in humans at the RHD of 20 mg/day.

When ponesimod was orally administered to female rats throughout pregnancy and lactation, decreased pup survival and body weight gain, and delayed sexual maturation were observed in the offspring at the highest dose tested. Fertility of the F1 females was reduced. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone K30
Silica colloidal anhydrous
Sodium laurilsulfate

Tablet coating

Hypromellose 2910
Lactose monohydrate
Macrogol 3350
Titanium dioxide
Triacetin

Ponvory 3 mg film-coated tablets
Iron oxide red (E172)
Iron oxide yellow (E172)

Ponvory 4 mg film-coated tablets
Iron oxide red (E172)
Black iron oxide (E172)

Ponvory 5 mg film-coated tablets
Black iron oxide (E172)
Iron oxide yellow (E172)

Ponvory 7 mg film-coated tablets
Iron oxide red (E172)
Iron oxide yellow (E172)

Ponvory 8 mg film-coated tablets
Iron oxide red (E172)
Black iron oxide (E172)

Ponvory 9 mg film-coated tablets
Iron oxide red (E172)
Black iron oxide (E172)
Iron oxide yellow (E172)

Ponvory 10 mg film-coated tablets
Iron oxide red (E172)
Iron oxide yellow (E172)

Ponvory 20 mg film-coated tablets
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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 or multipack containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/001
EU/1/21/1550/002
EU/1/21/1550/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 May 2021

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Patheon France
40 Boulevard De Champaret
38300 Bourgoin Jallieu
France

Creapharm Industry
29 rue Leon Faucher
51100 Reims
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Ponvory in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority. The MAH shall ensure that in each Member State where Ponvory is marketed, all healthcare professionals (HCPs) who intend to prescribe Ponvory are provided with a Healthcare Professional Information Pack, which contains the following:

- Information on where to find the latest Ponvory Summary of Product Characteristics (SmPC);
- Healthcare professional checklist;
- Patient/caregiver guide;
- Pregnancy-specific patient reminder card.

Healthcare professional checklist

The healthcare professional checklist shall contain the following key messages:

- Dose escalation at treatment initiation:
  - Start treatment on Day 1 with one 2-mg tablet orally once daily and progress with the 14-day titration schedule outlined in the following table:

Titration day	Daily dose
Days 1 and 2	2 mg
Days 3 and 4	3 mg
Days 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
Days 12, 13, and 14	10 mg

  After dose titration is complete, the recommended maintenance dose of Ponvory is one 20-mg tablet taken orally once daily.

- Re-initiation of Ponvory therapy following treatment interruption during dose titration or maintenance period:
  - If fewer than 4 consecutive doses are missed, resume treatment with the first missed dose.
  - If 4 or more consecutive doses are missed, re-initiate treatment with day 1 (2 mg) of the titration regimen (new treatment initiation pack).

  The same first-dose monitoring as for treatment initiation is recommended when 4 or more consecutive doses of Ponvory are missed during the titration or maintenance periods.

- Mandatory requirements before initiating treatment:

  Before first dose of Ponvory

  - Perform an electrocardiogram (ECG) to determine whether first-dose monitoring is needed. In patients with certain pre-existing conditions, first dose monitoring is recommended (see below).
  - Review results of a complete blood count (CBC) with differential (including lymphocyte count) obtained within 6 months prior to treatment initiation or after discontinuation of prior therapy.
  - Perform a liver function test (transaminases, bilirubin) within 6 months prior to treatment initiation.
  - Obtain an evaluation of the fundus, including the macula, prior to treatment initiation. Ponvory therapy should not be initiated in patients with macular oedema until resolution.

- A negative pregnancy test result must be available prior to treatment initiation in women of childbearing potential.
- Perform a varicella zoster virus (VZV) antibody test in patients without a HCP-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If negative, VZV vaccination is recommended at least 4 weeks prior to treatment initiation with Ponvory to allow the full effect of vaccination to occur.
- Initiation of treatment with Ponvory should be delayed in patients with severe active infection until resolution.
- Review 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 medicinal products, consider possible unintended additive effects on the immune system before treatment initiation.
- Determine whether patients are taking medicinal products that could slow down heart rate (HR) or atrioventricular (AV) conduction.

First-dose monitoring

- Recommended for patients with sinus bradycardia (HR <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 who are in stable condition.
- Monitor patients for signs and symptoms of bradycardia for 4 hours after the first dose 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.
- Extend the monitoring until resolution of findings if:
  - HR at 4 hours postdose is <45 bpm,
  - HR at 4 hours postdose is at the lowest value postdose, or
  - ECG at 4 hours postdose shows new onset second-degree or higher AV block.
- If pharmacological treatment is required, continue monitoring overnight and repeat 4-hour monitoring after the second dose.

- Cardiologist advice should be obtained before initiation of Ponvory in the following patients to determine overall benefit-risk and the most appropriate monitoring strategy:
  - Patients with significant QT prolongation (QTc >500 ms) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes).
  - Patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) anti-arrhythmic medicinal products.
  - 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, since significant bradycardia may be poorly tolerated in these patients, treatment is not recommended.
  - 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.
  - Patients with a history of recurrent syncope or symptomatic bradycardia.
  - Patients receiving concurrent therapy with drugs that decrease HR (e.g., beta-blockers, nondihydropyridine calcium channel blockers [diltiazem and verapamil], and other drugs that may decrease HR, such as digoxin); consider the need to switch to non-HR-lowering medicinal products. Concomitant use of these medicinal products during Ponvory initiation may be associated with severe bradycardia and heart block.

- Ponvory is contraindicated in the following patients:
  - Patients who have hypersensitivity to the active substance or to any of the excipients.
  - Patients in an immunodeficient state.

- Patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation, or New York Heart Association (NYHA) Class III/IV heart failure.
- Patients who have presence of Mobitz type II second-degree AV block, third-degree AV block, or sick-sinus syndrome, unless the patient has a functioning pacemaker.
- Patients with severe active infections and patients with active chronic infections.
- Patients with active malignancies.
- Patients with moderate or severe hepatic impairment (Child Pugh class B and C, respectively).
- Women who are pregnant and women of childbearing potential not using effective contraception.

- Ponvory reduces peripheral blood lymphocyte counts. Results of a CBC with differential (including lymphocyte count) obtained within 6 months prior to treatment initiation or after discontinuation of prior therapy should be reviewed in all patients prior to treatment initiation. Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2\times10^9$/L, if confirmed, should lead to interruption of Ponvory therapy until the level reaches $>0.8\times10^9$/L, after which re-initiation of Ponvory can be considered.

- Ponvory has an immunosuppressive effect that predisposes patients to infections, including opportunistic infections that can be fatal, and may increase the risk of developing malignancies, particularly those of the skin. Patients should be carefully monitored, especially those with concurrent conditions or known risk factors, such as previous immunosuppressive therapy. Discontinuation of treatment in patients at increased risk of infections or malignancies should be considered on a case-by-case basis.
  - Delay initiation of treatment with Ponvory in patients with severe active infections until resolved. Suspension of treatment during serious infection should be considered. Anti-neoplastic, immune-modulating, or immunosuppressive therapies should be co-administered with caution due to the risk of additive immune system effects, also for patients with a history of prior use. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration and the half-life and mode of action of medicinal products with prolonged immune effects should be considered when switching from these medicinal products.
  - Vigilance for skin malignancies is recommended. Caution patients against exposure to sunlight and UV light without protection. Patients should not receive concomitant phototherapy with ultraviolet B (UVB) radiation or psoralen and ultraviolet A (PUVA) photochemotherapy. Patients with pre-existing skin disorders and patients with new or changing skin lesions should be referred to a dermatologist to determine appropriate monitoring.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during treatment and for up to 1 week after the last dose of Ponvory. Physicians should also be vigilant for signs and symptoms of infection.
  - If cryptococcal meningitis (CM) is suspected, treatment with Ponvory should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

    Cases of fatal CM and disseminated cryptococcal infections have been reported in patients treated with other sphingosine-1-phosphate (S1P) receptor modulators.

  - Physicians should be vigilant for clinical signs and symptoms or magnetic resonance imaging (MRI) findings suggestive of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain caused by the John Cunningham polyoma virus. 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.

Cases of PML have been reported in patients treated with another S1P receptor modulator and other multiple sclerosis (MS) therapies.

- Use of live attenuated vaccines may carry a risk of infection and should therefore be avoided during treatment with Ponvory and up to 1 week after treatment discontinuation. If immunisation with a live attenuated vaccine is required, Ponvory treatment should be paused from 1 week prior to 4 weeks after a planned vaccination.

- An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients:
  - Prior to treatment initiation with Ponvory.
  - At any time if a patient reports any change in vision while on Ponvory therapy. Ponesimod therapy should not be initiated in patients with macular oedema until resolution. Patients who present with visual symptoms of macular oedema should be evaluated; if macular oedema is confirmed, treatment with Ponvory should be discontinued. After resolution of macular oedema, the potential benefits and risks of Ponvory should be considered before treatment re-initiation.
  - Patients with a history of uveitis or diabetes mellitus should have regular examinations of the fundus, including the macula, prior to treatment initiation with Ponvory, and have follow-up evaluations while receiving therapy.

- Ponvory is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
  - A negative pregnancy test result must be available in women of childbearing potential prior to treatment initiation; pregnancy testing must be repeated at suitable intervals during treatment.
  - Before initiation and during Ponvory treatment, women of childbearing potential should be counselled on the potential for a serious risk to the foetus during treatment with Ponvory, facilitated by the pregnancy-specific patient reminder card.
  - Women of childbearing potential must use effective contraception during treatment with Ponvory and for at least 1 week following treatment discontinuation.
  - Treatment with Ponvory must be discontinued at least 1 week before attempting to conceive.
  - Disease activity may return when treatment with Ponvory is discontinued due to pregnancy or attempting to conceive.
  - If a woman becomes pregnant during treatment, Ponvory must be immediately discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Ponvory treatment and follow-up examinations should be performed.
  - Ponvory should not be used during breast-feeding.
  - Physicians are encouraged to enrol pregnant patients in the Ponvory Pregnancy Outcomes Enhanced Monitoring (POEM), or pregnant women may enrol themselves.

- Elevation of transaminases and bilirubin may occur in patients taking Ponvory. Before treatment initiation, results of a liver function test obtained within the last 6 months should be reviewed. Patients who develop symptoms suggestive of hepatic dysfunction during treatment with Ponvory should be monitored for hepatotoxicity, and treatment should be discontinued if significant liver injury is confirmed (e.g., alanine aminotransferase [ALT] exceeds 3x upper limit of normal (ULN) and total bilirubin exceeds 2xULN).

- Ponvory may cause a decline in pulmonary function. Spirometry evaluation of respiratory function during treatment with Ponvory should be performed if clinically indicated.

- Blood pressure should be regularly monitored during treatment with Ponvory.

- Seizures have been reported in patients treated with Ponvory. Physicians should be vigilant for seizures, especially in those patients with a pre-existing history of seizures or a family history of epilepsy.

- Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an S1P receptor modulator. If a Ponvory-treated patient develops unexpected neurological or psychiatric signs or symptoms, signs or symptoms suggestive of increased intracranial pressure, or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled, and an MRI should be considered. 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, treatment with Ponvory should be discontinued.

Patient/caregiver guide

The Patient/Caregiver guide shall contain the following key messages:

- What Ponvory is and how it works.
- What multiple sclerosis is.
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it during treatment.
- Patients should have an ECG prior to receiving their first dose of Ponvory to determine whether first-dose monitoring is required. An ECG should also be done before treatment re-initiation when 4 or more consecutive doses are missed.
- When initiating treatment with Ponvory, patients should use a treatment initiation pack and should follow the 14-day titration schedule.
- Patients should immediately report any signs and symptoms indicative of slow HR (e.g., dizziness, vertigo, nausea, and palpitations) after the first dose of Ponvory to their prescriber.
- Patients should contact their prescriber in case of treatment interruption (i.e., 4 or more consecutive doses are missed). Patients should not restart treatment with Ponvory without seeking advice from their prescriber, as they may need to restart treatment with a new treatment initiation pack.
- Patients should have a recent (ie, within 6 months or after discontinuation of prior therapy) blood test of the blood cells prior to receiving their first dose of Ponvory.
- Patients who have not been infected with VZV (chickenpox) or who have not previously been vaccinated against VZV should be tested and if needed are recommended to be vaccinated at least 4 weeks prior to starting Ponvory treatment.
- Patients should immediately report any signs and symptoms of infection to their prescriber during Ponvory treatment and for up to 1 week after the last dose of Ponvory.
- The patient's vision should be checked prior to treatment initiation; patients should immediately report any signs and symptoms of visual impairment to their prescriber during Ponvory treatment and for up to 1 week after treatment ends.
- Ponvory must not be used during pregnancy or in women of childbearing potential who are not using effective contraception. Women of childbearing potential should:
    - Be informed by their prescriber about the risk of harmful effects to the foetus associated with Ponvory treatment both before treatment initiation and regularly thereafter.
    - Have a negative pregnancy test before starting treatment with Ponvory.
    - Use effective contraception during Ponvory treatment and for at least 1 week after treatment with Ponvory ends. Patients are advised to talk to their doctor about reliable methods of contraception.
    - Be informed by their prescriber that disease activity may return when treatment with Ponvory is stopped due to pregnancy or attempting to conceive.
    - Report immediately to their prescriber any pregnancy (intended or unintended) that occurs during Ponvory treatment or for up to 1 week after treatment with Ponvory ends.
    - Immediately stop Ponvory treatment if they become pregnant during treatment.
    - Not use Ponvory during breast-feeding.

Refer to the pregnancy-specific patient reminder card for further information and guidance related to contraception, pregnancy, and breast-feeding.

- Liver function tests should be performed prior to treatment initiation; patients should immediately report any signs or symptoms suggestive of hepatic dysfunction (e.g., nausea, vomiting, stomach pain, tiredness, loss of appetite, yellowing of the skin or the whites of the eyes, dark urine) to their prescriber.
- Patients should immediately report any signs or symptoms of new or worsening breathing problems (e.g., shortness of breath) to their prescriber.
- Blood pressure should be regularly monitored during treatment with Ponvory.
- Skin cancers have been reported in patients treated with Ponvory. Patients should limit their exposure to sunlight and UV light, for example, by wearing protective clothing and applying sunscreen with a high sun protection factor regularly. Patients should inform their prescriber immediately if any skin nodules (e.g., shiny, pearly nodules), patches, or open sores that do not heal within weeks develop. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape, or size over time.
- Patients should inform their prescriber about a pre-existing history or family history of epilepsy.
- Patients should immediately report any signs or symptoms suggestive of PRES (i.e., sudden severe headache, sudden confusion, sudden loss of vision or other changes in vision, seizure) to their prescriber.

Pregnancy-specific patient reminder card

The pregnancy-specific patient reminder card for women of childbearing potential shall contain the following key messages:

- Ponvory is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Prescribers will provide counselling before treatment initiation and regularly thereafter regarding the harmful effects to the foetus of Ponvory and required actions to minimize this risk.
- Women of childbearing potential must use effective contraception during Ponvory treatment and for at least 1 week after treatment ends. Patients are advised to talk to their doctor about reliable methods of contraception.
- A pregnancy test must be carried out and negative results verified by the prescriber before starting treatment with Ponvory. Pregnancy testing must be repeated at suitable intervals during treatment.
- If a woman becomes pregnant, suspects she is pregnant, or decides to become pregnant, treatment with Ponvory must be stopped immediately and medical advice regarding the risk of harmful effects to the foetus should be sought. Follow-up examinations should be performed. Patients should report immediately to their prescriber any pregnancy (intended or unintended) that occurs during Ponvory treatment or for up to 1 week after treatment with Ponvory ends.
- Ponvory must be stopped at least 1 week before attempting to conceive.
- Disease activity may return when treatment with Ponvory is stopped due to pregnancy or attempting to conceive.
- Women exposed to Ponvory during pregnancy are encouraged to join the Ponvory Pregnancy Outcomes Enhanced Monitoring (POEM) that monitors outcomes of pregnancy.
- Ponvory should not be used during breast-feeding.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TREATMENT INITIATION PACK

1. NAME OF THE MEDICINAL PRODUCT

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
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 mg film-coated tablet contains 2 mg of ponesimod

Each 3 mg film-coated tablet contains 3 mg of ponesimod

Each 4 mg film-coated tablet contains 4 mg of ponesimod

Each 5 mg film-coated tablet contains 5 mg of ponesimod

Each 6 mg film-coated tablet contains 6 mg of ponesimod

Each 7 mg film-coated tablet contains 7 mg of ponesimod

Each 8 mg film-coated tablet contains 8 mg of ponesimod

Each 9 mg film-coated tablet contains 9 mg of ponesimod or

Each 10 mg film-coated tablet contains 10 mg of ponesimod

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Treatment initiation pack

14 film-coated tablets

Each pack of 14 film-coated tablets for a 2-week treatment schedule contains:
2 film-coated tablets of Ponvory 2 mg
2 film-coated tablets of Ponvory 3 mg

2 film-coated tablets of Ponvory 4 mg
1 film-coated tablet of Ponvory 5 mg
1 film-coated tablet of Ponvory 6 mg
1 film-coated tablet of Ponvory 7 mg
1 film-coated tablet of Ponvory 8 mg
1 film-coated tablet of Ponvory 9 mg
3 film-coated tablets of Ponvory 10 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

OUTER WALLET TREATMENT INITIATION PACK

1. NAME OF THE MEDICINAL PRODUCT

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
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Treatment initiation pack

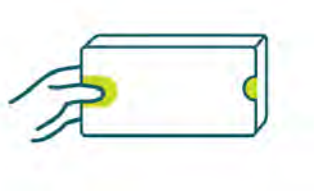
Each pack of 14 film-coated tablets for a 2-week treatment schedule contains:
2 film-coated tablets of Ponvory 2 mg
2 film-coated tablets of Ponvory 3 mg
2 film-coated tablets of Ponvory 4 mg
1 film-coated tablet of Ponvory 5 mg
1 film-coated tablet of Ponvory 6 mg
1 film-coated tablet of Ponvory 7 mg
1 film-coated tablet of Ponvory 8 mg
1 film-coated tablet of Ponvory 9 mg
3 film-coated tablets of Ponvory 10 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

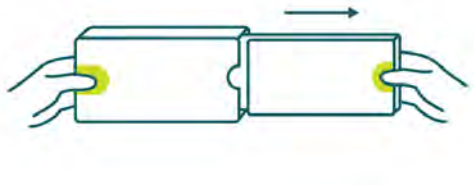
For oral use.

Read the package leaflet before use.

(1) Press and hold



(2) Pull out



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INNER WALLET TREATMENT INITIATION PACK

1. NAME OF THE MEDICINAL PRODUCT

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
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Take 1 tablet daily

Flip open

Fold over to close

Start date

Day 1, 2 mg
Day 2, 2 mg
Day 3, 3 mg
Day 4, 3 mg
Day 5, 4 mg
Day 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, 10 mg
Day 13, 10 mg
Day 14, 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TREATMENT INITIATION PACK (3 Blisters sealed in inner wallet)

1. NAME OF THE MEDICINAL PRODUCT

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
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of ponesimod.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

OUTER WALLET 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of ponesimod.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

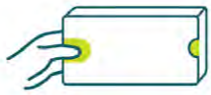
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

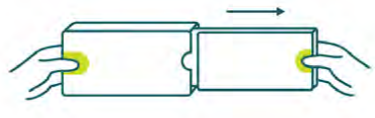
For oral use.

Read the package leaflet before use.

(1) Press and hold



(2) Pull out



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INNER WALLET 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

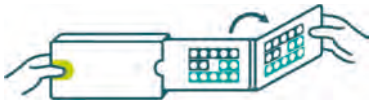
4. BATCH NUMBER

Lot

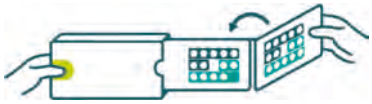
5. OTHER

Take 1 tablet daily

Flip open



Fold over to close



Start date
WEEK 1, 1, 2, 3, 4, 5, 6, 7
WEEK 2, 1, 2, 3, 4, 5, 6, 7
WEEK 3, 1, 2, 3, 4, 5, 6, 7
WEEK 4, 1, 2, 3, 4, 5, 6, 7

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 20 mg (2 Blisters sealed in inner wallet)

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 20 mg MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of ponesimod.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/003_____84 tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

OUTER WALLET 20 mg MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of ponesimod.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

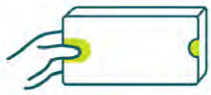
28 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

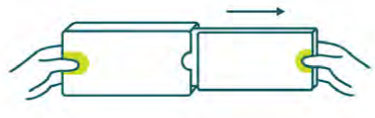
For oral use.

Read the package leaflet before use.

(1) Press and hold



(2) Pull out



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1550/003 84 tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ponvory 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INNER WALLET 20 mg MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

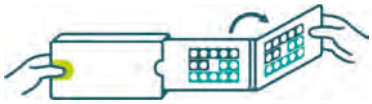
4. BATCH NUMBER

Lot

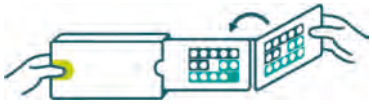
5. OTHER

Take 1 tablet daily

Flip open



Fold over to close



Start date
WEEK 1, 1, 2, 3, 4, 5, 6, 7
WEEK 2, 1, 2, 3, 4, 5, 6, 7
WEEK 3, 1, 2, 3, 4, 5, 6, 7
WEEK 4, 1, 2, 3, 4, 5, 6, 7

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 20 mg (2 Blisters sealed in inner wallet) MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film-coated tablets
ponesimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATOIRES JUVISE PHARMACEUTICALS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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
ponesimod

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ponvory is and what it is used for

What Ponvory is
Ponvory contains the active substance ponesimod. Ponesimod belongs to a group of medicines called sphingosine-1-phosphate (S1P) receptor modulators.

What Ponvory is used for
Ponvory is used to treat adults with relapsing forms of multiple sclerosis (RMS) with active disease. Active disease in RMS is when there are relapses or when MRI (magnetic resonance imaging) results show signs of inflammation.

What is multiple sclerosis
Multiple sclerosis (MS) affects the nerves in the brain and spinal cord (the central nervous system).

In MS, the immune system (one of the body's main defence systems) does not work properly. The immune system attacks a protective covering of nerve cells called myelin sheath – this causes inflammation. This breakdown of the myelin sheath (called demyelination) stops the nerves working properly.

Symptoms of MS depend on which part of the brain and spinal cord are affected. These can include problems with walking and balance, weakness, numbness, double vision and blurring, poor coordination and bladder problems.

Symptoms of a relapse may disappear completely when the relapse is over – but some problems may remain.

How Ponvory works
Ponvory reduces circulating lymphocytes, which are white blood cells involved in the immune system. It does this by keeping them in the lymphoid organs (lymph nodes). This means that fewer lymphocytes are available to attack the myelin sheath around the nerves in the brain and spinal cord.

Decreasing nerve damage in patients with MS reduces the number of attacks (relapses) and slows down worsening of the disease.

2. What you need to know before you take Ponvory

Do not take Ponvory if
- you are allergic to ponesimod or any of the other ingredients of this medicine (listed in section 6).
- your healthcare professional has told you that you have a severely weakened immune system
- you have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischaemic attack, TIA), or certain types of heart failure in the last 6 months
- if you have certain types of heart block (abnormal heart tracing on an ECG (electrocardiogram), usually with a slow heartbeat) or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker.
- you have severe active infection or active chronic infection
- you have active cancer
- you have moderate or severe liver problems
- you are pregnant or a woman of childbearing potential not using effective contraception.

If you are not sure if you have any of these apply to you, talk to your doctor before taking Ponvory.

Warnings and precautions
Talk to your doctor before taking Ponvory if:
- you have an irregular or abnormal or slow heartbeat
- you have ever had a stroke or other diseases related to blood vessels in the brain
- you have ever suddenly passed out or fainted (syncope)
- you have a fever or infection
- you have an immune system that does not work properly due to a disease or taking medicines that weaken your immune system.
- you have never had chickenpox (varicella) or have not received a vaccine for chickenpox. Your doctor may do a blood test for chickenpox virus. You may need to get the full course of vaccine for chickenpox and then wait 1 month before you start taking Ponvory.
- you have breathing problems (such as severe respiratory disease, pulmonary fibrosis or chronic obstructive pulmonary disease)
- you have liver problems
- you have diabetes. The chance of developing macular oedema (see below) is higher in patients with diabetes.
- you have eye problems – especially an inflammation of the eye called uveitis
- you have high blood pressure.

If any of the above apply to you (or you are not sure), talk to your doctor before taking Ponvory.

Tell your doctor straight away if you get any of the following side effects while taking Ponvory:

Slow heart rate (bradycardia or bradyarrhythmia)

Ponvory can slow down your heart rate – especially after you take your first dose. You should have an electrocardiogram (ECG, to check your heart's electrical activity) before you take your first dose of Ponvory or before you restart Ponvory after an interruption in treatment.

- If you are at increased risk for side effects due to a slowing of your heart rate, your doctor may monitor your heart rate and blood pressure for at least 4 hours after taking your first dose of Ponvory.
- You will also have an ECG at the end of the 4 hours. If you still have a very slow or decreasing heart rate, you may need to be monitored until these have resolved.

Infections

Ponvory can increase your risk of serious infections that can be life-threatening. Ponvory lowers the number of lymphocytes in your blood. These cells fight infection. Their numbers usually return to normal within 1 week of stopping treatment. Your doctor should review a recent blood test of your blood cells before you start taking Ponvory.

Call your doctor straight away if you have any of these symptoms of an infection during treatment with Ponvory or 1 week after your last dose of Ponvory:

- fever
- tiredness
- body aches
- chills
- nausea
- vomiting
- headache with fever, neck stiffness, sensitivity to light, nausea, confusion, (these may be symptoms of meningitis, an infection of the lining around your brain and spine).

Macular oedema

Ponvory can cause a problem with your vision called macular oedema (build-up of fluid in the back of the eye (retina) that may cause changes in vision, including blindness).

The symptoms of macular oedema can be similar to vision symptoms of a MS attack (called optic neuritis). Early on, there may not be any symptoms. Be sure to tell your doctor about any changes in your vision. If macular oedema happens, it usually starts in the first 6 months after you start taking Ponvory.

Your doctor should check your vision before you start taking Ponvory and also anytime you notice vision changes during treatment. Your risk of macular oedema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

Call your doctor straight away if you have any of the following:

- blurriness or shadows in the centre of your vision
- a blind spot in the centre of your vision
- sensitivity to light
- unusually coloured (tinted) vision.

Liver problems

Ponvory may cause liver problems. Your doctor should do blood tests to check your liver function before you start taking Ponvory.

Call your doctor straight away if you have any of the following symptoms of liver problems:
- nausea
- vomiting
- stomach pain
- tiredness
- loss of appetite
- your skin or the whites of your eyes turn yellow
- dark urine.

Increased blood pressure

As Ponvory can increase your blood pressure, your doctor should check your blood pressure regularly during treatment with Ponvory.

Exposure to the sun and protection against the sun

As Ponvory may increase the risk of skin cancer, you should limit your exposure to sunlight and UV (ultraviolet) light, by:
- wearing protective clothing
- regularly applying sunscreen with high sun protection factor.

Breathing problems

Some people who take Ponvory have shortness of breath. Call your doctor straight away if you have new or worsening breathing problems.

Swelling and narrowing of the blood vessels in your brain

A condition called PRES (posterior reversible encephalopathy syndrome) has happened with medicines acting similarly to Ponvory. Symptoms of PRES usually improve when you stop taking Ponvory. However, if left untreated, it may lead to a stroke.

Call your doctor straight away if you have any of the following symptoms:
- sudden severe headache
- sudden confusion
- sudden loss of vision or other changes in your vision
- seizure.

Worsening of multiple sclerosis after stopping Ponvory

When Ponvory is stopped, symptoms of MS may return. They may be worse compared to before or during treatment. Always talk to your doctor before you stop taking Ponvory. Tell your doctor if you have worsening symptoms of MS after stopping Ponvory.

Children and adolescents
Ponvory has not been studied in children and adolescents, therefore it is not recommended for use in children and adolescents aged less than 18 years.

Other medicines and Ponvory
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- medicines to control your heart rhythm (antiarrhythmics), blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers medicines that may slow your heart rate).

- medicines that affect your immune system, due to a possible additive effect on the immune system.

Vaccines and Ponvory
Tell your doctor if you have recently received any vaccinations or if you are planning to receive a vaccination. You should avoid receiving live vaccines during treatment with Ponvory. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Ponvory should be stopped 1 week before and for 4 weeks after receiving a live vaccine. Also, other vaccines may not work as well when given during treatment with Ponvory.

Pregnancy, contraception, and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

- Do not use Ponvory during pregnancy. If Ponvory is used during pregnancy there is a risk of harm to your unborn baby.
- Do not use if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception.

Women of childbearing potential/Contraception in females

If you are a woman of childbearing potential:
- Your doctor will inform you about the risk of harm to your unborn baby before you start treatment with Ponvory and you should have a pregnancy test to check that you are not pregnant.
- You must use effective contraception while taking Ponvory and for 1 week after you stop taking it.

Talk to your doctor about reliable methods of contraception.

If you do become pregnant while taking Ponvory, stop taking Ponvory and tell your doctor straight away.

If you become pregnant within 1 week after you stop taking Ponvory, talk to your doctor.

Breast-feeding

You should not breast-feed while you are taking Ponvory. This is to avoid a risk of side effects for the baby since Ponvory may pass into breast milk.

Driving and using machines
Ponvory is not expected to have an influence on your ability to drive and use machines.

Ponvory contains lactose
Ponvory contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Ponvory contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Ponvory

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

How to take

- Take Ponvory exactly as your doctor tells you. Do not change your dose or stop taking Ponvory unless your doctor tells you to.
- **Take only 1 tablet each day.** To help you remember to take your medicine you should take it at the same time each day.
- Take with or without food.

Treatment initiation pack (14-day)

- **Only** start your treatment with Ponvory using the treatment initiation pack, with which your dose will be gradually increased over 14 days. The purpose of the titration phase is to reduce any side effects due to slowing your heart rate at the start of treatment.
- Write down the date you start taking the medicine next to day 1 on the Ponvory treatment initiation pack.
- Follow this 14-day treatment schedule.

Treatment initiation pack day	Daily dose
Day 1	2 mg
Day 2	2 mg
Day 3	3 mg
Day 4	3 mg
Day 5	4 mg
Day 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	10 mg
Day 13	10 mg
Day 14	10 mg

Maintenance dose

- **After** you finish taking the tablets in the treatment initiation pack, continue treatment using the 20 mg maintenance dose.
- Write down the date you start taking the 20 mg maintenance dose, next to week 1 of the Ponvory 20 mg blister pack.

If you take more Ponvory than you should

If you have taken more Ponvory than you should, call your doctor straight away or go to a hospital straight away. Take the medicine pack and this package leaflet with you.

If you forget to take Ponvory

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

- If you miss taking up to 3 Ponvory tablets in a row, while taking the treatment initiation pack or the maintenance dose, you can continue treatment by taking the **first** dose you missed. Take **1** tablet as soon as you remember, then take 1 tablet a day to continue with the treatment initiation pack dose or maintenance dose as planned.
- If you miss 4 or more Ponvory tablets in a row, while taking the treatment initiation pack or the maintenance dose, you need to restart treatment with a new 14-day treatment initiation pack. Call your doctor straight away if you miss 4 or more doses of Ponvory.

Write down the date you start taking the medicine so you will know if you miss 4 or more doses in a row.

Do not stop taking Ponvory without talking with your doctor first.
Do not restart Ponvory after stopping it for 4 or more days in a row without seeking advice from your doctor. You will need to restart your treatment with a new treatment initiation pack.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be or could become **serious**

Tell your doctor or pharmacist immediately if you notice any of the side effects listed below because they may be signs of serious effects:

Common (may affect up to 1 in 10 people)
- urinary tract infection
- bronchitis
- flu (influenza)
- viral infection of nose, throat, or chest (viral respiratory tract infection)
- viral infection
- herpes zoster virus infection (shingles)
- lung infection (pneumonia)
- spinning sensation (vertigo)
- fever (pyrexia)
- build-up of fluid in the back of the eye (retina) that may cause changes in vision, including blindness (macular oedema)
- fits (seizures)

Uncommon (may affect up to 1 in 100 people)
- slow heart beat (bradycardia)

Other side effects

Very common (may affect more than 1 in 10 people)
- infection of the nose, sinuses, or throat (nasopharyngitis, respiratory tract infection)
- increased level of liver enzymes in the blood (a sign of liver problems)
- low number of a type of white blood cell, called lymphocytes (lymphopenia)

Common (may affect up to 1 in 10 people)
- high blood pressure (hypertension)
- back pain
- feeling very tired (fatigue)
- feeling dizzy
- being short of breath (dyspnoea)
- high level of cholesterol in the blood (hypercholesterolaemia)
- joint pain (arthralgia)
- arm or leg pain
- depression
- difficulty sleeping (insomnia)
- cough
- itchy, runny, or blocked nose (rhinitis), infected or irritated throat (pharyngitis, laryngitis), sinus infection (sinusitis)
- feeling anxious (anxiety)

- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- increased level of a protein in the blood that may indicate an infection or inflammation (C-reactive protein increased)
- feeling sleepy (somnolence)
- indigestion (dyspepsia)
- swollen hands, ankles, or feet (peripheral oedema)
- migraine
- ligament sprain
- chest discomfort

Uncommon (may affect up to 1 in 100 people)
- high level of potassium in the blood (hyperkalaemia)
- swollen joint
- dry mouth

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ponvory

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister foil after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ponvory contains
- The active substance is ponesimod

- The other excipients are:
  Tablet core

  Croscarmellose sodium, lactose monohydrate (see “Ponvory contains lactose”), magnesium stearate, microcrystalline cellulose, Povidone K30, silica colloidal anhydrous and sodium laurilsulfate.

  Tablet coating

  Hypromellose 2910, lactose monohydrate, Macrogol 3350, titanium dioxide and triacetin.

  Ponvory 3 mg film-coated tablets
  Iron oxide red (E172) and iron oxide yellow (E172)

  Ponvory 4 mg film-coated tablets
  Iron oxide red (E172) and black iron oxide (E172)

Ponvory 5 mg film-coated tablets
Black iron oxide (E172) and iron oxide yellow (E172)

Ponvory 7 mg film-coated tablets
Iron oxide red (E172) and iron oxide yellow (E172)

Ponvory 8 mg film-coated tablets
Iron oxide red (E172) and black iron oxide (E172)

Ponvory 9 mg film-coated tablets
Iron oxide red (E172) and black iron oxide (E172), iron oxide yellow (E172)

Ponvory 10 mg film-coated tablets
Iron oxide red (E172) and iron oxide yellow (E172)

Ponvory 20 mg film-coated tablets
Iron oxide yellow (E172)

What Ponvory looks like and contents of the pack
Ponvory 2 mg film-coated tablets are 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 are 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 are 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 are 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 are 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 are 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 are 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 are 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 are 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 are 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.

Ponvory treatment initiation pack (wallet configuration)

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) (wallet configuration)

Pack containing 28 film-coated tablets for a 4-week treatment schedule or in a multipack containing 84 (3 packs of 28) film-coated tablets for a 12-week treatment schedule.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
LABORATOIRES JUVISE PHARMACEUTICALS
149 Boulevard Bataille de Stalingrad
69100 Villeurbanne
France

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Patheon France
40 Boulevard De Champaret
38300 Bourgoin Jallieu
France

Creapharm Industry
29 rue Leon Faucher
51100 Reims
France

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu