SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ponvory 20 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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)
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 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 medicinal products 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.

Infections

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 treatment discontinuation in the setting of PML, patients should be monitored for development of immune reconstitution inflammatory syndrome (PML-IRIS) (see above).

Excipients with known effect

Lactose

This medicinal product 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 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 medical 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 Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 x 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 randomisation, 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 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.

Ponvory 20 mg film-coated tablets (maintenance pack)

Pack of 28 film-coated tablets.

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)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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