Summary of the Risk Management Plan (RMP) for PONVORY® (Ponesimod)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of PONVORY® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the product information «Arzneimittelinformation / Information sur le medicament» approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of PONVORY ® in Switzerland is the «Arzneimittelinformation / Information sur le medicament» (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of PONVORY®.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Ponvory (ponesimod)

This is a summary of the Core Risk Management Plan (RMP) and Swiss-specific Annex for Ponvory. The RMP details important risks of Ponvory, how these risks can be minimized, and how more information will be obtained about Ponvory's risks and uncertainties (missing information).

Ponvory's Swissmedic-approved product information gives essential information to healthcare professionals (HCPs) and patients on how Ponvory should be used.

Newly identified safety concerns and changes to existing safety concerns are included in updates to the Ponvory RMP and the Swiss-specific Annex for Ponvory.

I. The Medicine and What it is Used For

Ponvory is authorized for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. It contains ponesimod as the active substance and it is given by oral administration. Treatment is initiated as a 14-day up-titration regimen starting with one 2-mg tablet, followed by administration of 3-, 4-, 5- 6-, 7-, 8-, 9-, and 10-mg tablets over 14-day period. Following initial dose titration, the daily regimen is one 20-mg tablet.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Ponvory, together with measures to minimize such risks and the proposed studies for learning more about Ponvory's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the CPPI and CCDS addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit-Risk Evaluation Report (PBRER) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ponvory is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Ponvory are risks that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ponvory. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long- term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Bradyarrhythmia occurring post-first dose Macular edema Bronchoconstriction Convulsions
Important potential risks	Severe liver injury Serious opportunistic infections including PML Skin cancer Non-skin malignancy Reproductive and embryofetal toxicity Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)
Missing information	Use in elderly patients Long-term safety of ponesimod

II.B. Summary of Important Risks

Important Identified Risk: Bradyarrhythmia occurring post-first dose	
Evidence for linking the risk to the medicine	In guinea pigs, single doses of ponesimod ≥0.3 mg/kg/day induced atrioventricular (AV) blocks and decreased heart rate (HR). These cardiovascular effects were significantly reduced on repeat dosing and after a low starting dose and up-titration (desensitization). Transient HR reductions and, less frequently, transient first- or second-degree AV block have been observed in the first days of treatment with ponesimod during the clinical development program. Bradycardia was identified as an adverse reaction. These findings and this adverse reaction are described in the CCDS.
Risk factors and risk groups	Risk factors include cardiac rhythm disorders or electrocardiogram (ECG) abnormalities indicative of an increased risk for arrhythmia,

	low resting HR, history of fainting or collapse, significant QT prolongation (i.e., QT corrected [QTc] >500 ms), and concurrent therapy with anti-arrhythmic medicinal products, QT prolonging medicinal products, or medicinal products that slow HR. Patients with pre-existing cardiovascular comorbidities (such as ischemic heart disease, cardiac failure and history of cardiac arrest or myocardial infarction, cerebrovascular disease, uncontrolled hypertension, and presence of AV block) are also at increased risk.
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CCDS: Contraindications • CCDS: Warnings and precautions • CCDS: Interactions • CCDS: Adverse Reactions • CCDS: Overdose • CCDS: Pharmacodynamic Properties • CPPI Section 2 • CCPI Section 3 • CPPI Section 4 • An ECG should be obtained before treatment initiation with ponesimod as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 2. • Ponesimod treatment must be started with a 14-day up-titration scheme using a starter pack as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 3

	• Advice from a cardiologist should be sought before treatment initiation with ponesimod if treatment is considered in patients with certain pre-existing heart conditions, as described in in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions'. • First-dose monitoring is recommended for patients with certain heart conditions, as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 2. • Appropriate management should be initiated in case certain post-dose heart-related disorders or symptoms occur, as described in CCDS Section 'Dosage and Administration'. • Advice from a cardiologist should be sought before treatment initiation with ponesimod if treatment is considered in patients who receive concomitant therapy with medicinal products that decrease HR, as described in CCDS Sections 'Dosage and Administration', 'Warnings and Precautions', and 'Interactions'. • Patients with overdosage of ponesimod, especially upon initiation/re-initiation of treatment, should be observed for signs and symptoms of bradycardia as well as AV conduction blocks, which may include overnight monitoring, as described in CCDS Section 'Overdose'. • Pack size: ponesimod treatment initiation pack for 14-day up-titration • Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Macular edema	
Evidence for linking the risk to the medicine	Cases of macular edema associated with changes in visual acuity have been reported in subjects treated with ponesimod during the clinical development program and macular edema was identified as an adverse reaction. This adverse reaction is described in the CCDS.
Risk factors and risk groups	Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of developing macular edema during therapy with sphingosine-1-phosphate (S1P) receptor modulators.
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CCDS: Warnings and Precautions • CCDS: Adverse Reactions • CPPI Section 2 • CPPI Section 4 • An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before ponesimod treatment initiation and again at any time if a patient reports any change in vision while on ponesimod therapy, as described in CCDS Sections ‘Dosage and Administration’ and ‘Warnings and Precautions’ and CPPI Section 2. • Regular follow-up examinations of the fundus, including the macula, should be performed during ponesimod treatment in patients with a history of uveitis or diabetes mellitus, as described in CCDS Section ‘Warnings and Precautions’. • Patients who experience symptoms of macular edema should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important Identified Risk: Bronchoconstriction	
Evidence for linking the risk to the medicine	In rats, a dose- and time-dependent effect on respiratory function was seen. The functional effect was characterized by a decrease in the relaxation time with a slight increase in the peak expiratory flow and tidal volume (increase in Penh), which indicates a transition from passive to more active expiration. Adverse events suggestive of bronchoconstriction and changes in pulmonary function in the form of a decrease in forced expiratory volume in 1 second (FEV_1) have been reported in subjects treated with ponesimod during the clinical development program. Dyspnea and cough were identified as adverse reactions. These findings and adverse reactions are described in the CCDS.
Risk factors and risk groups	No specific risk factors for bronchoconstriction have been identified.
Risk minimization measures	Routine risk minimization measures: • CCDS: Warnings and Precautions • CCDS: Adverse Reactions • CCDS: Pharmacodynamic Properties • CPPI Section 2 • CPPI Section 4 • Spirometry evaluation of respiratory function should be performed during ponesimod therapy, if clinically indicated, as described in CCDS Section 'Warnings and Precautions'. • Patients who develop new or worsening breathing problems should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Convulsions	
Evidence for linking the risk to the medicine	Cases of convulsions have been reported in subjects treated with ponesimod during the clinical development program and are described in the CCDS. It is unknown whether these events were related to the effects of multiple sclerosis, to ponesimod, or to a combination of both.
Risk factors and risk groups	No clear predisposing factors for convulsions could be identified.
Risk minimization measures	Routine risk minimization measures: • CCDS: Adverse Reactions • CPPI Section 2 • Patients who experience symptoms of a seizure should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Severe liver injury	
Evidence for linking the risk to the medicine	As seen with other S1P receptor modulators, liver enzyme elevations, such as increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in subjects treated with ponesimod during the clinical development program and were identified as adverse reactions. These adverse reactions are described in the CCDS. Overall, the majority of ALT and AST elevations occurred within 6 or 12 months after ponesimod treatment initiation. There were no Hy's law cases in the ponesimod clinical program. Most cases of ALT increases ≥3x upper limit of normal were single transient asymptomatic episodes and resolved on continued ponesimod treatment; the rest resolved upon study treatment discontinuation.
Risk factors and risk groups	No specific risk factors for severe liver injury have been identified.
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CCDS: Warnings and Precautions • CCDS: Adverse Reaction • CCDS: Pharmacokinetic Properties • CPPI Section 2 • CPPI Section 4 • Recent (i.e., within the last 6 months) transaminase and bilirubin levels should be reviewed before treatment initiation with ponesimod, as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 2. • Patients who develop symptoms suggestive of hepatic dysfunction should be monitored for hepatotoxicity. Ponesimod treatment should be discontinued in case significant liver injury is confirmed, as described in CCDS Section 'Warnings and Precautions'.
	• Patients who develop symptoms of liver problems should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Serious opportunistic infections including PML	
Evidence for linking the risk to the medicine	Cases of infections have been reported in subjects treated with ponesimod during the clinical development program. Several types of infection were identified as adverse reactions. These findings and adverse reactions are described in the CCDS. No cases of fatal infections have been reported in subjects treated with ponesimod during the clinical development program; however, life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators.
Risk factors and risk groups	Patients in an immunodeficient state and those with severe active infections or active chronic infections are at increased risk for developing serious opportunistic infections including progressive multifocal leukoencephalopathy (PML).
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CCDS: Warnings and Precautions • CCDS: Interactions • CCDS: Adverse Reactions • CPPI Section 2 • CPPI Section 4

	• Results from a recent (i.e., within 6 months or after discontinuation of prior therapy) complete blood count (CBC) with differential (including lymphocyte count) should be reviewed before treatment initiation with ponesimod, as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 2. • Treatment initiation with ponesimod should be delayed in patients with severe active infection until resolution. Vigilance for signs and symptoms of infection should be continued for 1 to 2 weeks after treatment discontinuation, as described in CCDS Section 'Warnings and Precautions'. • Effective diagnostic and therapeutic strategies should be used in patients with symptoms of infection while on ponesimod therapy. Suspension of ponesimod treatment should be considered if a patient develops a serious infection, as described in CCDS Section 'Warnings and Precautions'. • Patients without an HCP-confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before treatment initiation with ponesimod, as described in CCDS Sections 'Dosage and Administration' and 'Warnings and Precautions' and CPPI Section 2. • Physicians should be vigilant for clinical signs or symptoms of cryptococcal meningitis (CM). Patients with signs or symptoms 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, as described in CCDS Section 'Warnings and Precautions'. • Physicians should be vigilant for clinical symptoms or magnetic resonance imaging findings suggestive of PML. If PML is suspected, ponesimod treatment should be suspended until PML is excluded, as described in CCDS Section 'Warnings and Precautions'.

	• The half-life and mode of action of medicinal products with prolonged immune effects should be considered when switching from these medicinal products to avoid unintended additive effects on the immune system, as described in CCDS Sections 'Warnings and Precautions' and 'Interactions'. • A full course of vaccination with varicella vaccine is recommended for antibody-negative patients before treatment initiation with ponesimod, as described in CCDS Sections 'Dosage and Administration', 'Warnings and Precautions', and CPPI Section 2. • The use of live, attenuated vaccines should be avoided while on ponesimod therapy. If immunization with a live attenuated vaccine is required, ponesimod treatment should be paused from 1 week prior to 4 weeks after a planned vaccination, as described in CCDS Sections 'Warnings and Precautions' and 'Interactions' and CPPI Section 2. • Patients who experience symptoms of infection should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Skin cancer	
Evidence for linking the risk to the medicine	Cases of skin cancer, including basal cell carcinoma and a case of malignant melanoma, have been reported in subjects treated with ponesimod during the clinical development program and are described in the CCDS. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator.
Risk factors and risk groups	Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing skin cancer. There is also well-established scientific support for an association between ultraviolet radiation and skin cancer; sunlight can also cause immunosuppression.
Risk minimization measures	Routine risk minimization measures: • CCDS: Adverse Reactions • CPPI Section 4

	• Patients treated with ponesimod should be cautioned against exposure to sunlight without protection, and they should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy, as described in CCDS Section 'Adverse Reactions' and CCPI Section 4. • Legal status: available by prescription only
	Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Non-skin malignancy	
Evidence for linking the risk to the medicine	Rare cases of non-skin malignant neoplasms (including solid tumors and hematologic tumors) have been reported in subjects treated with ponesimod during the clinical development program.
Risk factors and risk groups	Patients in an immunodeficient state and patients with a history of malignancies have an increased risk of developing non-skin malignancy.
Risk minimization measures	Routine risk minimization measures: • Legal status: available by prescription only
	Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Reproductive and embryofetal toxicity	
Evidence for linking the risk to the medicine	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ponesimod-induced developmental toxicity, including an increase in malformations (skeletal and visceral) and embryolethality. The area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) in rats and rabbits at the no-observed-adverse-effect level (1 mg/kg/day in both species) are lower than the human systemic exposures at the recommended human dose of 20 mg/day. Ponesimod has not been studied in pregnant women. Clinical trials of ponesimod excluded pregnant and breast-feeding women. Clear recommendations how to avoid pregnancies in women of childbearing potential are described in the CCDS. Based on human experience in patients receiving another S1P receptor modulator, postmarketing data suggest that its use is associated with an increased risk of major congenital malformations.
Risk factors and risk groups	Women of childbearing potential who do not use effective contraception are at risk.
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CCDS: Contraindications • CCDS: Warnings and Precautions • CCDS: Pregnancy and Breast-feeding • CCDS: Nonclinical Information • CPPI Section 2 • Before initiation of ponesimod treatment in women of childbearing potential, a negative pregnancy test result must be available, as described in CCDS Sections ‘Dosage and Administration’ and ‘Pregnancy and Breastfeeding’ and CPPI Section 2.

	• Women of childbearing potential should be counseled before treatment initiation on the potential for a serious risk to the fetus and the need for effective contraception during treatment with ponesimod and for 1 week after treatment discontinuation, as described in CCDS Sections 'Warnings and Precautions' and 'Pregnancy and Breastfeeding' and CPPI Section 2. • Ponesimod treatment should be discontinued immediately if a woman becomes pregnant during treatment, as described in CCDS Section 'Pregnancy and Breast-feeding' and CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Ponesimod Pregnancy Outcomes Enhanced Monitoring (POEM) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)	
Evidence for linking the risk to the medicine	No cases of posterior reversible encephalopathy syndrome (PRES) or acute disseminated encephalomyelitis (ADEM) have been reported in subjects treated with ponesimod during the clinical development program. However, rare cases of PRES have been reported in patients receiving other S1P receptor modulators. In clinical trials of another S1P receptor modulator, rare events involving the nervous system, including ischemic and hemorrhagic strokes and neurological atypical disorders such as ADEM-like events, occurred in patients treated at higher doses.
Risk factors and risk groups	Many patients with PRES have potentially severe comorbidities such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension, which may be predisposing factors. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES, and patients with renal dysfunction appear to be at higher risk of developing PRES.

Risk minimization measures	Routine risk minimization measures: • CCDS: Warnings and Precautions • CPPI Section 2 • A complete physical and neurological examination should be scheduled in ponesimod-treated patients who develop any unexpected neurological or psychiatric symptoms/signs, any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, and magnetic resonance imaging should be considered, as described in CCDS Section 'Warnings and Precautions'. • If PRES is suspected, ponesimod treatment should be discontinued, as described in CCDS Section 'Warnings and Precautions'. • Patients who experience symptoms suggestive of PRES should call their physician immediately, as described in CPPI Section 2. • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in elderly patients	
Risk minimization measures	Routine risk minimization measures: • CCDS: Dosage and Administration • CPPI Section 2 • Legal status: available by prescription only Additional risk minimization measures: • None

Missing Information: Long-term safety of ponesimod	
Risk minimization measures	Routine risk minimization measures: • Legal status: available by prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial AC-058B303/OPTIMUM-LT • Trial AC-058B202 See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Ponvory.

II.C.2. Other Studies in Postauthorization Development Plan

Ponesimod Pregnancy Outcomes Enhanced Monitoring (POEM).

Purpose of the study: To evaluate the potential risk of reproductive and embryofetal toxicity in pregnant women exposed to ponesimod.

The objective of this study is to prospectively collect and evaluate safety data on pregnancy outcomes and on the risk of birth defects in the offspring of women exposed to ponesimod immediately before (up to 1 week before last menstrual period) and during pregnancy.

AC-058B303/OPTIMUM-LT: A multicenter, non-comparative extension to study AC-058B301 to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis.

Purpose of the study: To characterize the long-term safety of ponesimod and control of disease in subjects with RMS and to investigate the effect on disease activity in a relatively large population after a brief interruption.

The objectives of this trial are to describe the long-term safety and tolerability of ponesimod 20 mg in subjects with RMS as well as the effects of re-initiation of ponesimod treatment after interruption in subjects with RMS.

AC-058B202: A multicenter, randomized, double-blind, parallel-group extension to study AC-058B201 to investigate the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod, an oral $S1P_1$ receptor agonist, in patients with relapsing-remitting multiple sclerosis.

Purpose of the study: To investigate the long-term safety, tolerability, and efficacy of ponesimod.

The objective of this trial is to investigate the long-term safety and tolerability of ponesimod.