Date: 21 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ponvory

International non-proprietary name: ponesimod
Pharmaceutical form: film-coated tablets
Dosage strengths: 20 mg, 10 mg, 9 mg, 8 mg, 7 mg, 6 mg, 5 mg, 4 mg, 3 mg, 2 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Janssen-Cilag AG
Marketing Authorisation No.: 68114
Decision and Decision date: approved on 16 November 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

1-ABT	1-Aminobenzotriazole
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALC	Absolute peripheral lymphocyte count
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARR	Annual relapse rate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
AUCinf	Area under the plasma concentration-time curve from time 0 to infinity
BCRP	Breast cancer resistance protein
BID	Twice a day
BMI	Body mass index
Bpm	Beats per minute
CDA	Confirmed disability accumulation
CI	Confidence interval
CIs	Confidence intervals
CIS	Clinically isolated syndrome
CL/F	Apparent Clearance
Cmax	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CPN	Chronic progressive nephropathy
CUAL	Combined unique active lesions
CYP	Cytochrome P450
DLCO	Diffusion lung capacity for carbon monoxide
DMTs	Disease modifying therapies
ECG	Electrocardiogram
eCRF	Electronic Case Report form
EDSS	Expanded Disability Status Scale
EOS	End of study
ERA	Environmental Risk Assessment
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
FSIQ-RMS	Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis
GC	Gas chromatography
Gd+	Gadolinium enhancing
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
hERG	Human ether-à-go-go-related gene
HI	Hepatic impairment
HPLC	High-performance liquid chromatography
HR	Heart rate
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IPC	In-process control
IR	Infrared
IV	Intravenous
LC-MS/MS	Liquid Chromatography coupled to Mass Spectrometry
LoQ	List of Questions

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MAH	Marketing Authorisation Holder
Max	Maximum
MD	Multiple dose
Min	Minimum
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
N/A	Not applicable
NEDA	No evidence of disease activity
NO(A)EL	No Observed (Adverse) Effect Level
OATP	Organic anion transport polypeptide
OR	Odds ratio
PD	Protocol deviations
PgP	P-glycoprotein
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
Pon	Ponesimod
PopPK	Population PK
PPMS	Primary progressive multiple sclerosis
PPND	Pre- and postnatal development
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RMP	Risk Management Plan
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
RT	Retention time
SAEs	Serious adverse events
SD	Single dose
SmPC	Summary of product characteristics
S1P1	Sphingosine 1-phosphate receptor type 1
S1P5	Sphingosine 1-phosphate 5 receptor
SPMS	Secondary progressive multiple sclerosis
SwissPAR	Swiss Public Assessment Report
TEAEs	Treatment-emergent adverse events
Tmax	Time to reach Cmax
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
ULN	Upper limit of normal
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
Vss	Volume of distribution at steady state

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance ponesimod of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Ponvory is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS)

2.2.2 Approved Indication

Ponvory is indicated for the treatment of adult patients with relapsing remitting forms of multiple sclerosis (RRMS) with active disease defined by clinical or imaging features

2.2.3 Requested Dosage

A starter pack must be used for all patients initiating treatment with ponesimod, with a 14-day titration starting with one 2 mg tablet orally once daily and progressing as shown in Table 20.

Dose Titration regimen

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

Interruption during treatment, especially during titration, should be avoided; however, if treatment titration is interrupted and <4 consecutive doses are missed, treatment should be resumed with the first missed dose. If 4 or more consecutive doses are missed, treatment should be reinitiated starting from Day 1 of the titration regimen (i.e. a new starter pack).
After treatment titration is complete, the recommended maintenance dosage of ponesimod is one 20 mg tablet taken orally once daily. If 4 or more consecutive daily doses are missed during maintenance treatment, treatment should be reinitiated starting from Day 1 of the titration regimen (i.e. a new starter pack).
(For full text dosage recommendations see *information for healthcare professionals*)

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	31 July 2020
Formal control completed	27 August 2020
List of Questions (LoQ)	22 December 2020
Answers to LoQ	22 March 2021
Predecision	18 June 2021
Answers to Predecision	17 August 2021
Final Decision	16 November 2021
Decision	approval

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3 Medical Context

Multiple sclerosis (MS) is a chronic, predominantly immune-mediated inflammatory disease of the central nervous system (CNS), affecting approximately 2.8 million individuals worldwide (MS International Federation, 2021).
MS is characterised by autoreactive lymphocytes that attack and destroy the myelin sheath surrounding nerve cells, resulting in demyelination, axonal damage and disruption of the blood-brain barrier, causing neurological impairment and severe disability.
The prevalence is 100-200 per 100,000 inhabitants. Around 15,000 people with MS live in Switzerland (CH) (United Nations Department of Economic and Social Affairs, 2019) and the prevalence has increased over the last years. The annual incidence is circa 3.5–5 per 100,000 inhabitants (CH: 4.0–5.5/100,000) and is increasing according to data from Scandinavian registries.
Clinically, MS starts in approximately 85% of patients as relapsing remitting MS (RRMS), with variable disease activity interspersed with periods of stability. The onset of RRMS typically occurs between the ages of 20 and 40 and predominantly affects women (2 to 3 times more frequently than men).
Approximately 70% of patients with RRMS develop, within the first 10 to 15 years after diagnosis, a secondary progressive MS (SPMS), which is characterised by worsening of disability in the absence or independent of relapses.
Relapsing forms of MS (RMS) include patients with RRMS, patients with clinically isolated syndrome (CIS – refers to the first clinical event and evidence of dissemination of lesions in time and space on the magnetic resonance imaging (MRI) scan) and those with SPMS with superimposed relapses. There are no clear criteria that mark the transition from RRMS to SPMS.
Additionally, around 15% of patients demonstrate progressive neurological deterioration without superimposed relapses at the beginning of the disease. This form is called primary progressive MS (PPMS), begins typically in the 4th or 5th decade of life and affects men equally as women.
The current therapeutic approach of treating RMS involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies (DMTs). The goal of a DMT is to modify the natural course of disease by reducing the rate of relapses and MRI disease activity, and delay disability progression. There are a number of DMTs available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles, but there is still no cure available for MS.
Sphingosine 1-phosphate (S1P) receptor modulation has been shown to be a highly effective treatment for MS (Brinkman, 2010). Antagonism of S1P receptor type 1 (S1P1) inhibits the egress of lymphocytes from lymph nodes, thereby decreasing circulating lymphocytes (Scott, 2016; Tran, 2017), and preclinical evidence suggests that S1P1 and sphingosine 1-phosphate 5 receptor (S1P5) modulation also may have direct CNS effects resulting in reduction of inflammatory cytokines, demyelination, and axonal loss, and preservation of GABAergic transmission. (Gentile, 2016; Groves, 2013; Slowik, 2015).
Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator. Ponesimod binds with high affinity to the S1P receptor 1 located on lymphocytes. It induces a rapid (within hours of dosing) and dose-dependent reduction in the peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis may involve the reduction of lymphocyte migration into the central nervous system.

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4 Quality Aspects

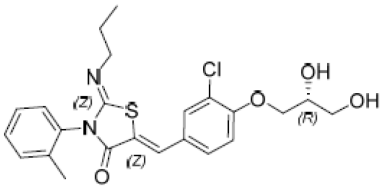
4.1 Drug Substance

INN: Ponesimod
Chemical name: (2Z,5Z)-5-[3-chloro-4-[(2R)-2,3-dihydroxypropoxy]benzylidene]-3-(2- methylphenyl)-2- (propylimino)-1,3-thiazolidin-4-one

Molecular formula: $C_{23}H_{25}ClN_2O_6S$

Molecular mass: 460.97 g/mol

Molecular structure:



Physico-chemical properties:
Ponesimod is a white to light yellowish powder. Ponesimod exhibits stereoisomerism due to the presence of one chiral centre. The absolute configuration at the single stereocentre is (R). Different polymorphic forms were identified throughout development. Ponesimod is poorly soluble in aqueous media in the pH range of 1-7.5. Due to its properties, ponesimod is considered to be a biopharmaceutics classification system (BCS) class 2 compound. Ponesimod is non-hygroscopic in nature.

Synthesis:
Ponesimod is synthesised in three steps using well-defined starting materials with acceptable specifications. The synthesis of the drug substance has been adequately described. The critical steps and in-process controls as well as intermediates are adequately defined and deemed suitable for controlling the manufacturing process. The specifications for the starting materials and intermediates are acceptable. Quality of reagents, solvents and auxiliary materials used in the manufacturing process of ponesimod are adequately controlled for the intended use. Development of the ponesimod route of synthesis has been discussed in suitable detail, including process iterations and optimisations from lab to production scale. Changes introduced have been presented in sufficient detail and have been justified.

Structure elucidation:
The structure of ponesimod has been fully elucidated using several analytical techniques, including FT-IR, 1H-NMR and 13C-NMR, MS, UV and X-ray powder diffraction. Potential impurities have been adequately discussed.

Specification:
The active substance specification is set according to ICH Q6A and includes tests for appearance, identity by IR, residue on ignition, residual solvents (GC), impurities (HPLC), assay (HPLC) and particle size distribution (laser light diffraction). Limits for impurities are set according to ICH Q3A and considered appropriate. The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Results for three consecutive validation commercial batches of the API manufactured in compliance with the proposed synthesis pathway at the commercial manufacturing site have been provided. The same drug substance batches are used in manufacturing of drug product registry batches. The analytical results are in full compliance with the specified limits and show only little variability with respect to the

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individual parameters tested, thus demonstrating a reliable and reproducible manufacturing process with consistent results from batch to batch.

Reference standards:
Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Container-closure system:
The container-closure system for the final API is adequately described and its suitability is assured.

Stability:
Results from stability studies on 3 batches of production scale of the micronised API manufactured by the commercial manufacturing chain and in the commercial packaging concept are provided. Based on the obtained results, the proposed 48-month re-test period for ponesimod drug substance if stored below 30 °C in the proposed container closure system can be accepted. Photostability testing following the ICH guideline Q1B was performed on one batch. Based on the results provided, ponesimod is photosensitive and should be stored protected from light.

4.2 Drug Product

Description and composition:
The finished drug product is supplied as immediate-release film-coated tablets for oral use at 10 dosage strengths, containing 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg or 20 mg of ponesimod as active substance. Different dosage strengths are needed due the titration of the active substance at the beginning of treatment. The different strengths are distinguished by size, colour and debossing. The final drug products are adequately described. The description is in compliance with information presented in Module 1 and the information for healthcare professionals.

Pharmaceutical development:
The excipients chosen are typical for this type of dosage form and used in common quantities. Formulation and manufacturing development have been adequately described overall. All excipients are well-known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Bioequivalence between the formulations was demonstrated clinically. The revised dissolution method used in development and quality-control (QC) is systematically and acceptably described overall, and the discriminatory power is demonstrated. A systematic and scientific approach was followed for the development of the manufacturing process of the final tablets. Within this approach, critical process parameters have been adequately considered, and results from design of experiments (DoE) studies have been adequately discussed and demonstrate that the manufacturing process is well understood. Based on the outcome of these studies, critical process parameters have been identified and critical control points have been defined and target points set, and these have been used to define suitable in-process controls (IPCs).

Manufacture:
Manufacturing of the final tablets can basically be considered as a common standard process involving wet granulation, drying, sieving, blending, compression and coating. However, due to the low content of ponesimod, manufacturing of the 5 mg strength (unit dose products containing drugs in low content (≤ 2% of composition)) is a non-standard method. Overall, an acceptable description of the manufacturing process is provided. The provided IPCs established for the manufacturing process are acceptable and justified. The critical steps in manufacturing have been evaluated during process development and are presented in section P.2.3. A suitable risk assessment is presented during development. Validation studies have been designed based on the outcome of this evaluation. The bracketing approach for validation studies proposed by the applicant is acceptable. Detailed test results are provided and demonstrate that the manufacturing process is basically under control.

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Specification:
The tested parameters at release (including IPC) and shelf-life are in compliance with the Ph. Eur. monograph “tablets” and ICH-Guideline CPMP/ICH/367/96. For identification of the API, two different analytical methods are used. Specified limits for assay at release and shelf-life are in-line with 3AQ11A. No significant decrease during storage is observed. Specification limits for impurities are in line with current regulatory guidelines (CPMP/ICH/2738/99-ICH Q3B (R2). The specification limit for the dissolution specification is in compliance with EMA’s reflection paper EMA/336031/2017 and can therefore be accepted.

Some of the analytical methods used in quality control of the intermediate and the medicinal product are based on Ph. Eur. or are standard methods that do not need to be described in detail. The analytical in-house methods used for release and shelf-life are adequately described, and validity is demonstrated. The provided batch results at release, together with the results obtained from development and stability testing, confirm the consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug product. Degradation products are adequately characterised, and a suitable discussion on elemental impurities and the risk of N-nitrosamines is provided.

Container closure system:
The presented primary packaging system Alu/Alu blister with integrated desiccant is standard for solid formulations. The proposed container closure system is acceptably described, and its suitability is demonstrated.

Stability:
Appropriate stability data have been generated for the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established. The storage recommendation is “Do not store above 30°C. Store in the original package to protect the contents from moisture. Keep out of the reach of children”.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been shown.

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5 Nonclinical Aspects

The nonclinical development programme for Ponvory with the new active substance ponesimod followed relevant ICH guidelines. The pivotal studies for safety were performed in compliance with GLP regulations.

5.1 Pharmacology

In vitro, ponesimod was shown to be an $S1P_1$ (sphingosine 1-phosphate receptor 1) agonist (EC_{50} 5.7 nM). Ponesimod was also an agonist of $S1P_3$ (EC_{50} = 108 nM) and $S1P_5$ (EC_{50} = 69 nM) receptors but had no activity on $S1P_2$ or $S1P_4$ receptors. Whereas the magnitude of the maximal response to ponesimod was comparable to that elicited by the natural ligand S1P, ponesimod was 4-fold more potent on the $S1P_1$ receptor and 154-times less potent on the $S1P_3$ receptor. The major human metabolite M13 was 138-fold less potent on $S1P_1$ than ponesimod and therefore expected to be pharmacologically inactive.

In vivo, ponesimod temporarily reduced lymphocyte counts in mice, rats, dogs, and cynomolgus monkeys in a dose-dependent manner. In different animal models of lymphocyte-mediated diseases in mice (autoimmune encephalomyelitis as a model for MS; models for skin delayed-type hypersensitivity and systemic lupus erythematosus) and rats (adjuvant-induced arthritis), ponesimod prevented the induced disease or improved the health status by anti-inflammatory effects associated with a decrease in the number of circulating lymphocytes.

In a secondary pharmacodynamic screening assay on a panel of 107 different targets, no substantial off-target activity of ponesimod (10 µM) was identified. The off-target activity of M13 was not evaluated. This is accepted since M13 has been adequately characterised in the repeat-dose toxicity studies.

Ponesimod was evaluated in a core battery of *in vitro* and *in vivo* studies to assess effects on cardiovascular, respiratory and central nervous system (CNS) function according to ICH S7A/B. As cardiovascular adverse effects are known from other S1P receptor agonists, multiple additional *in vitro* and *in vivo* models were used to assess cardiac safety. Ponesimod *in vitro* showed no relevant inhibition of the hERG channel and had *in vivo* no effect on the QT interval. Therefore, the risk for induction of cardiac arrhythmias is considered low. In guinea pigs, ponesimod induced decreases in heart rate (bradycardia) and atrioventricular blocks. In rats and dogs, ponesimod-related increases in blood pressure were observed. The blood pressure increase in dogs was related to vasoconstriction, which was identified as the cause of the arteriopathy noted in the left heart ventricle in the chronic toxicity study (see below). Ponesimod-related effects on respiratory function were seen after single- and multiple-dose studies in rats. Bradycardia, increased blood pressure, and decreased pulmonary function are identified risks of ponesimod treatment similar to other S1P modulators. Neurological function in rats was not affected by ponesimod. In dogs, CNS findings were observed at exposures that are 42-fold higher than the clinical exposure at 20 mg/kg daily (based on AUC).

5.2 Pharmacokinetics

Pharmacokinetics of ponesimod was studied in rats and dogs. Oral bioavailability was ≥ 35% in rats and ≥ 57% in dogs. Systemic plasma clearance was low in rats and dogs, with a gender difference observed in rats (higher clearance in males). Elimination half-lives were 1.7 – 3.6 hours in rats and 8.7 – 11 hours in dogs, i.e. shorter than in humans (33 h).

Following repeated daily dosing in rats and dogs, systemic exposure to ponesimod generally increased dose-proportionally. Exposure to ponesimod was higher in female than in male rats (≈ 2- fold), whereas no sex-difference was noted in mice and dogs. There was no accumulation in any of the nonclinical species.

In vitro plasma protein binding of ponesimod and M13 was high (≥ 99%) across all animal species and humans. In rats, [^{14}C]-ponesimod-related radioactivity was widely distributed in most tissues, crossed the blood brain barrier, and was excreted in milk. It transiently bound to melanin-containing tissues in the pigmented rat.

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The *in vitro* metabolic profile of ponesimod was investigated in liver microsomes and hepatocytes of mice, rats, dogs, and humans. Metabolism in liver microsomes was very limited in all species whereas significant transformation was observed in incubations with hepatocytes. No unique metabolites were identified in human hepatocytes. *In vivo*, ponesimod was extensively metabolised. Unchanged ponesimod was the major component in plasma samples in rats, dogs, and humans. The most abundant human plasma metabolites M12 and M13 were also identified in rats and dogs, which were sufficiently exposed. Ponesimod was primarily eliminated by metabolism via the biliary/faecal route in rats and dogs, similar to the route of elimination in humans.

5.3 Toxicology

The toxicological profile of ponesimod was evaluated in mice, rats, rabbits (reproductive toxicity), and dogs. The selection of rat and dog for toxicological assessment is considered appropriate as both species are pharmacologically relevant and the metabolism of ponesimod is comparable to that in humans. The route of administration and frequency of dosing in the nonclinical studies are consistent with the proposed clinical setting (once daily oral dosing).

Pivotal repeat-dose oral toxicity studies were conducted up to 26 weeks in rats (doses: 0, 0.4, 4, 30 and 100 mg/kg/day) and up to 52 weeks in dogs (doses: 0, 1, 3 and 10 mg/kg/day). A 13-week study was conducted in mice (doses: 0, 10, 30 and 90 mg/kg/day) for dose selection for the carcinogenicity study.

Repeated doses of 400 mg/kg/day in rats and ≥ 100 mg/kg/day in dogs resulted in mortality (rats) and moribund condition and CNS effects (dogs). As expected from the pharmacological mode of action of ponesimod, the main target organ was the immune system in all species. Changes in the lymphoid system (decreased lymphocyte counts in peripheral blood with corresponding atrophic changes in lymph nodes, spleen and thymus) were noted at the lowest doses independently of the treatment duration. As these changes are related to the desired therapeutic effect, they were not considered adverse by the applicant. Additional organs of toxicity were the lung (weight increase, alveolar histiocytes associated with alveolar hyalinosis: mouse, rat, dog) and the heart (arteriopathy: dog). Ponesimod-related changes were also noted in liver (weight increase, centrilobular hypertrophy, clinical pathology changes: mice, rats, and dogs), adrenal gland (weight increase, cortical fatty change, increased lipid concentration: rat), and skin (sores correlating with inflammatory changes: dog). These occurred at dose levels providing acceptable safety margins and were therefore considered adaptive, not adverse, and/or were linked to the immunomodulatory pharmacology of ponesimod. Except for the heart findings in dogs, the changes showed a tendency to reversibility or were reversible after the recovery periods.

In the carcinogenicity study in rats, ponesimod-related effects were also noted in the kidneys (increased incidence of chronic progressive nephropathy, CPN) and brain (focal cerebral necrosis and brain mineralisation). Pathogenesis of the brain necrosis is probably multifactorial, secondary to CPN and related to a ponesimod-related effect on blood pressure and ion channels, including calcium channels. Ponesimod-associated brain mineralisation was reported only in rats and was not observed in other nonclinical species (dogs and mice). This finding is considered rat-specific and related to an exaggerated pharmacologic class effect of S1P modulators. Overall, the mineralisation and secondary changes are considered not clinically relevant.

The exposures (AUC) at the NOAELs in the chronic toxicity studies were 5.6-fold (male rat) and 4-fold (dog) the clinical exposure at the recommended dose of 20 mg/day. The low safety margins can be accepted considering the proposed indication.

Ponesimod tested negative for genotoxic potential *in vitro* and *in vivo* according to ICH S2 (R1).

Ponesimod was not carcinogenic in rats at doses up to 30 and 100 mg/kg/day in males and females, respectively, corresponding to 3.6-fold and 18.7-fold the clinical exposure. In mice, at an $AUC_{0\text{-}24}$ value that is 2.4 times the clinical exposure, the incidence of vascular tumours (haemangioma and haemangiosarcoma) was increased. Vascular tumours have also been described in mice following treatment with other $S1P_1$ modulators, including fingolimod (Gilenya), ozanimod (Zeposia), and

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siponimod (Mayzent). The clinical relevance is unclear, which is reflected in the information for healthcare professionals.

Ponesimod did not affect the fertility of male or female rats at doses up to 100 mg/kg/day, which corresponds to an exposure ≥ 18-fold the clinical exposure. In embryo-foetal development studies, marked embryo-foetal toxicity and teratogenicity occurred in rats in the absence of maternal toxicity at ≥ 10 mg/kg/day. In rabbits, minimal maternal toxicity and an increase in post-implantation loss occurred at the highest dose administered (4 mg/kg/day). In the pre- and postnatal developmental (PPND) toxicity study in rats, ponesimod was well tolerated and did not induce maternal toxicity during gestation and/or lactation. In the F1 generation, pup survival and weight gain, as well as female fertility, were decreased at the high dose of 20 mg/kg/day, and sexual maturation was delayed in both genders at all doses tested. The exposures at the NOAELs in the embryo-foetal development and PPND studies are below or within the clinical exposure. The risks are adequately reflected in the information for healthcare professionals.

A study in juvenile rats (treatment with up to 100 mg/kg/day from Day 28 to Day 91 of age according to the PIP did not indicate any specific concerns for the paediatric population.

Ponesimod induced an impaired immunogenic response to the administration of a T-cell dependent antigen. Therefore, immune impairment, increased infection risk and effects on vaccination cannot be excluded. Appropriate warnings and recommendations are included in the information for healthcare professionals.

Ponesimod tested negative for phototoxic potential in the *in vitro* 3T3 Neutral Red uptake test. Abuse or dependency liabilities are not expected.

Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns about excipients.

Based on the preliminary ERA provided with the application, the risk for the environment is considered low. Submission of the reports on additional studies and an updated ERA were requested as a post-marketing commitment.

The summary of the nonclinical studies in the RMP is considered adequate. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

5.4 Nonclinical conclusions

In conclusion, a comprehensive study package covering pharmacology, pharmacokinetics and toxicology has been submitted to characterise the pharmaco-toxicological profile of ponesimod. All nonclinical data that are relevant for safety are mentioned in the information for healthcare professionals. From the nonclinical point of view, the application is approvable.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption and Biopharmaceutical Development

Ponesimod is categorised as a biopharmaceutical classification system (BCS) class II drug of low solubility and high permeability.

Capsules and tablets were employed in the course of the clinical development programme. The tablets are the proposed commercial formulation.

The absolute bioavailability of the tablet was 83.8 % after fasted administration. The metabolite/parent ratio for M12 and M13 was similar after i.v. and oral administration, indicating a low first pass metabolism.

The capsules and tablets (40 mg strength) were bioequivalent with regard to ponesimod AUC. The ponesimod absorption was faster after administration of the tablets (median tmax 4 h versus 5 h, Cmax 27% ↑).

The administration of the capsule with a high fat, high calorie breakfast resulted in a prolongation of the median ponesimod tmax from 2.5 h to 5.0 h. Ponesimod Cmax and AUCinf were not affected.

The effect of food on the absorption of the proposed commercial formulation was not formally investigated in a bioavailability study. However, data from a pop PK analysis indicated a similar ponesimod exposure after fed and fasted administration.

The available data support the administration of ponesimod independently of food.

Dose Proportionality
After administration of single doses between 1 mg and 75 mg, the ponesimod exposure increased proportionally to the administered dose.

After multiple once daily (QD) administration of doses between 5 mg and 40 mg, a slightly more than dose proportional increase of ponesimod exposure was observed.

After dose titration up to 100 mg QD, a slightly less than dose proportional increase of the ponesimod exposure was observed. This was also the case for the M12 Cmax. The M12 AUC0-24h and the M13 Cmax and AUC0-24h increased proportionally to the administered doses.

Pharmacokinetics after multiple Dosing
Ponesimod reached its steady state after 4 days of QD dosing. A 2.0- to 2.6-fold accumulation was observed after QD dosing. Both findings were in agreement with a half-life of about 30 h.

Distribution

The mean in vitro plasma-protein binding of ponesimod was 99.6% and was independent of concentration over the investigated range of 100 to 200,000 ng/mL.

The overall mean in vitro blood/plasma ratio of ponesimod was 0.68, and the average plasma partition coefficient was 78.5%, indicating no significant uptake of ponesimod into blood cells. The *in vitro* data were in reasonable agreement with the findings after administration of a ^{14}C-labelled dose to healthy subjects (blood/plasma ratio about 0.4).

Ponesimod *in vitro* binding to human serum albumin and to alpha-1-acid glycoprotein was 98.7-98.8% and 94.4-95.5%, respectively.

The *in vitro* plasma protein binding of M13 was 99% and was independent of concentration over the investigated range of 0.1 to 20 µg/mL. The mean blood/plasma ratio of M13 was 0.50.

The *in vitro* plasma protein binding of M12 was not investigated.

The ponesimod fraction unbound (fu) was slightly higher in subjects with mild or moderate hepatic impairment compared to healthy controls, but there was no consistent trend of increasing fu with decreasing hepatic function. It increased with decreasing renal function.

The ponesimod volume of distribution (Vss) after intravenous administration was 160 L.

Metabolism - In vitro Data

In the presence of the pan-CYP inhibitor 1-ABT, M12 formation in hepatocytes was reduced by approximately two-thirds, whereas M13 formation was undiminished, indicating that M13 formation was independent of both CYPs and M12 formation.

The formation of M12 involved a 2-step metabolic pathway through an initial, reversible, formation of a glyceraldehyde intermediate metabolite. CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12 were involved in the formation of M12.

The formation of M13 involved an initial, reversible formation of a hydroxyketone intermediate. The formation of the M13 precursor intermediate hydroxyketone appeared to be CYP independent. No other recombinant human Phase 1 enzymes (i.e. flavin-dependent monooxygenases 1, 3, and 5, monoamine oxidases A and B) and subcellular fractions (mitochondria and dehydrogenase-containing cytosol) metabolised ponesimod to a detectable extent. The enzymes involved in the formation of M13 could not be identified.

The two glucuronides M10 and M11 were mainly formed by UGT1A1 and 2B7, with lower rates observed for UGTs 1A3, 1A4, and 2B4.

Both M12 and M13 were not pharmacologically active.

Metabolism - Clinical Data

After administration of a single ^{14}C-labelled ponesimod dose, the only metabolites identified in plasma were M12 and M13. However, the AUC0-inf of the total radioactivity in plasma was about 2.6-fold higher than the sum of the radioactivity due to ponesimod, M12 and M13. The half-life of the total radioactivity in plasma was considerably longer than the half-lives of ponesimod, M12 or M13. The raw data indicated a high fraction of unidentified radioactivity in plasma.

The existence of additional unidentified metabolites is therefore likely. Qualitative investigations of steady state metabolite (plasma) data indicated a similar metabolite profile after single and multiple dosing over 14 days.

Based on “cold” LC-MS/MS measurements, ponesimod, M12 and M13 accounted for 73.8%, 5.9% and 20.2%, respectively, of the total exposure in plasma after multiple dosing.

In urine, 23 metabolites were detected and 12 of them were identified. The major component was an unidentified peak ‘f’ (RT: 12.8 minutes), representing 7% of the radioactivity recovered in urine. In

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addition, seven identified metabolites (including M12) and six unidentified peaks were detected with an abundance between 1–5% of the total radioactivity recovered in urine. All other detected metabolites (including M13) accounted for less than 1% of the urinary radioactivity. Unchanged ponesimod was not found in urine samples.

In faeces, 21 metabolites and the parent drug were quantified, and all but one were identified. Unchanged ponesimod and M12 were the major components detected, representing approximately 26% and 22%, respectively, of the radioactivity recovered in faeces. In addition, 12 identified metabolites were detected with an abundance between 1–5% of the radioactivity recovered in faeces. All other metabolites (seven) accounted for less than 1% of the faecal radioactivity.

Elimination
After administration of a single ^{14}C-labeled ponesimod dose, 10.3% - 18.4% and 57.3% - 79.6% of the radioactive dose, respectively, were excreted in urine and faeces. The total recovery was between 71.9% and 91.3%.

The half-life of ponesimod and M12 was about 30 hours. The half-life of M13 was about 38 hours.

Special Populations

Compared to healthy controls, there were 1.33-, 2.01- and 3.07- fold increases in ponesimod AUC0-inf in subjects with mild, moderate or severe hepatic impairment (HI), respectively. The mean ponesimod half-life increased with decreasing hepatic function, from 31.6 h in healthy subjects to 80.5 h in subjects with severe hepatic impairment (Child Pugh C). Ponesimod Cmax and tmax were not affected by hepatic function.

Both M12 and M13 were affected by hepatic function as well:

M12:
Cmax ↔, 1.81-fold ↑, 2.38-fold↑ in subjects with mild, moderate or severe HI, respectively.
AUCinf 1.3-fold ↑, 4.27-fold ↑, 5.57-fold↑ in subjects with mild, moderate or severe HI, respectively.

The median tmax was similar in healthy controls and subjects with mild or moderate HI, but increased from about 4 h to 24 h in subjects with severe HI. The half-life increased from 38 h in healthy controls to 93.5 h in subjects with severe HI.

M13:
Cmax about 40 % ↓ in subjects with mild or moderate HI, ↔ in subjects with severe HI
AUCinf 1.24-fold ↑, 1.7-fold ↑, 2.14-fold↑ in subjects with mild, moderate or severe HI

The median tmax was similar in healthy controls and subjects with HI of all degrees. The half-life increased from 36 h in healthy controls to 110 h in subjects with severe HI.

Moderate or severe renal impairment had no effect on ponesimod PK. Moderate renal impairment had no effect on the exposures to M12 and M13 but, in subjects with severe renal impairment, an 1.83-fold or 1.86-fold increase in M12 or M13 AUC0-tlast was observed. Both metabolites' median tmax was 24 h in subjects with renal impairment compared to 17 h in subjects with normal renal function.

The ponesimod exposure was similar in weight-matched Japanese and Caucasian subjects. No gender differences in ponesimod exposure were observed.

The potential impact on ponesimod PK was investigated in the context of a pop PK analysis for the following factors:

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Patient status (healthy subject, MS patient or psoriasis patient), food, formulation, hepatic impairment, race, renal impairment, gender, age, height and body weight.

The pop PK dataset included 680 subjects, of whom 255 (37%) were healthy and 340 (50%) were MS patients. The overall age range of the subjects in the dataset was 17 – 65 years. The age range of the MS patients was 18 – 55 years.

The final model included the following covariate relationships:

- Food status (fed versus fasted) and formulation (capsule versus tablet) on Tlag
- Body weight, psoriasis (versus healthy), and MS (versus healthy) on Vc/F
- Body weight and race (Black versus White) on Vp/F
- Body weight, race (Black versus White), and HI on CL/F

The final model described the data reasonably well. Apart from hepatic impairment, the impact of the covariates on ponesimod exposure was within the range of the inter-individual variability.

The available PK data support the dosing recommendations for special populations.

Interactions

Effect of other Drugs on Ponesimod

Several CYPs (CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12) were involved in the formation of M12, while the enzymes involved in the formation of M13 (the “main metabolite”) could not be identified.

Ponesimod was not a substrate for Pgp, BCRP, OATP1B1 or OATP1B3. M13 was a substrate for BCRP, OATP1B1 and OATP1B3. Data regarding M13 being a substrate for Pgp were not available.

The interaction potential of ponesimod as a victim appeared to be low.

Effect of Ponesimod on other Drugs

In vitro Data

Inhibition of CYPs and UGTs

The *in vivo* interaction risk assessment based on current regulatory guidelines indicated a potential to inhibit **intestinal CYP3A4**, but ponesimod had no clinically relevant effect on the exposure of ethinyl estradiol and norethisterone .

Induction of CYPs

The assessment of the possibility of an *in vivo* induction of CYP3A4 by ponesimod indicated a low risk.

Inhibition of Transporters

The risk assessment according to current regulatory guidelines indicated a potential of ponesimod to inhibit **intestinal BCRP** *in vivo*.

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Clinical Data

Affected Compound	GMR (90% CI)
Ethinyl Estradiol (EE)	EE Cmax: 0.94 (0.86-1.03) EE AUC_{0-24h}: 0.95 (0.89-1.01)
Norethisterone (NOR)	NOR Cmax: 0.87 (0.80-0.94) NOR AUC_{0-24h}: 0.84 (0.76-0.93)
Propranolol (PROP)	**2 mg PON (SD)** PROP Cmax: 88.61 (77.42-101.42) PROP AUCtau: 93.18 (84.88 – 102.30) **20 mg PON (MD)** PROP Cmax: 107.92 (93.00 – 125.24) PROP AUCtau: 110.67 (99.84- 122.68)
4-OH-Propranolol (OH-PROP)	**2 mg PON (SD)** OH-PROP Cmax: 99.61 (85.94-115.45) OH-PROP AUCtau: 98.85 (85.82-113.86) **20 mg PON (MD)** OH-PROP Cmax: 95.31 (81.02-112.12) OH-PROP AUCtau: 111.03 (95.00 – 129.76)

Pharmacodynamics

SECONDARY PHARMACOLOGY (SAFETY)

Effect on Heart Rate

Like all S1P1 receptor modulators, ponesimod caused bradycardia at the beginning of the treatment, which is, in most cases, attenuated by dose titration, but is also enhanced by other compounds affecting heart rate.

Two studies to evaluate several up-titration regimens to attenuate the bradycardia at treatment start caused by ponesimod were conducted in healthy subjects.

In the first study, the following titration regimens were investigated:

2.5 mg BID for 3 days, followed by 5 mg BID for 3 days, followed by 20 mg QD for 3 days
5 mg BID for 3 days, followed by 10 mg QD for 3 days, followed by 20 mg QD for 3 days
10 mg QD for 3 days followed by 20 mg QD for 3 days

Furthermore, the heart rate after a drug holiday of 1-3 days and treatment re-initiation with 20 mg was investigated.

The data indicated that the regimen starting with 2.5 mg BID provided the best attenuation of the initial bradycardia and that 10 mg QD was suboptimal as a starting dose.

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With regard to the treatment re-initiation after a drug holiday of 1-3 days, the heart rate change from baseline on the re-initiation day increased with increasing duration of the drug holiday. However, the differences to the preceding dose of 20 mg were quite small, supporting a drug holiday of < 4 days.

In the second study, the following titration regimen was investigated:

Day 1: placebo QD
Days 2–3: 2 mg QD
Days 4–5: 3 mg QD
Days 6–7: 4 mg QD
Day 8: 5 mg QD
Day 9: 6 mg QD
Day 10: 7 mg QD
Day 11: 8 mg QD
Day 12: 9 mg QD
Days 13–14: 10 mg QD
Day 15: 20 mg QD

This corresponded mostly to the proposed up-titration scheme. The only difference was the administration of 10 mg QD for only two days in the study compared to 3 days in the proposed titration scheme.

The second titration scheme investigated was as follows:

Day 1: placebo QD
Days 2–8: 10 mg QD
Day 9: 20 mg QD
Days 10–15: placebo QD

The titration regimen starting with 2 mg QD was superior with regard to heart rate, PR changes, the occurrence of AV blocks, and the occurrence of other electrocardiogram (ECG) abnormalities.

The superiority of the “2 mg QD” regimen was also supported by a pop PKPD analysis investigating the relationship between ponesimod exposure and heart rate (HR). The analysis included nine Phase 1 studies in healthy subjects and covering a wide dose range. The final PKPD model included body mass index (BMI) and sex as covariates of baseline HR (↑ with increasing BMI and in women) and age as a covariate on the circadian time shift of HR (daily HR maximum occurred later in older subjects.

The model described the data sufficiently well to be suitable for simulations. Of the three simulated titration regimens, the “2 mg QD” regimen was predicted to cause the lowest incidence of bradycardia.

Effect on QTc

The potential impact of ponesimod on QTcI was investigated after up-titration up to 40 mg QD and 100 mg QD, respectively. The ponesimod Cmax after 100 mg QD was about 2-fold higher compared to 40 mg QD. As the proposed therapeutic dose is 20 mg QD, about 4-fold higher Cmax values were achieved in the tQT study.

After up-titration to 40 mg or 100 mg, ponesimod had no effect on heart rate on the two days of ECG measurements.

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Ponesimod caused a concentration dependent QTcI prolongation at supra-therapeutic exposure. After 40 mg QD, the upper limit of the 90% CI did not exceed 10 ms, but came with 9.1 ms at 4 h post-dose quite close. After 100 mg QD, the upper limit of the 90% CI exceeded 10 ms at several time points. Based on the available data, a clinically relevant QTc prolongation at therapeutic exposure (=> after 20 mg QD) appears to be unlikely.
Moxifloxacin showed the expected effect, i.e. assay sensitivity was demonstrated.

No QTcI prolongations > 500 ms or QTcI changes from baseline > 60 ms were observed. The highest percentage of subjects with QTcI changes from baseline > 30 ms was observed after 100 mg ponesimod compared to the other treatments.

PKPD analyses confirmed the positive linear relationship between ponesimod, M12 and M13 plasma concentrations and QTcI. The metabolites, especially M13, appeared to be the main driver of the effect on QTcI.

Ponesimod had no effect on the PR or QRS interval at the investigated doses.

PHARMACODYNAMIC INTERACTIONS WITH OTHER MEDICINAL PRODUCTS OR SUBSTANCES

In a dedicated interaction study, a single dose of 10 mg ponesimod was administered alone or combined with atenolol or diltiazem after multiple dosing. The study was stopped for safety reasons after the occurrence of three cardiovascular SAEs (two AV blocks of 2nd or 3rd degree, one life-threatening collapse with 1 minute of asystole). Because of the small number of available subjects, no comparative statistical evaluation of the data could be done, but both atenolol and diltiazem had an additive effect on the bradycardia due to ponesimod.

In another pharmacodynamic study, potential interactions between propranolol and ponesimod were investigated with both compounds at steady state and after up-titration of the ponesimod dose up to 20 mg QD. Again, an additive effect of the beta blocker on the bradycardia caused by ponesimod was observed. It was most pronounced after the first dose of ponesimod and decreased over time despite the increasing ponesimod dose. A comparison of propranolol alone versus propranolol plus ponesimod also showed a statistically significant additive effect on heart rate, but the differences between the treatments were much smaller than for the comparison ponesimod alone versus ponesimod plus propranolol.

There were more abnormalities in the PR interval after 20 mg ponesimod compared to 2 mg, but the addition of propranolol did not appear to further increase the incidence of these findings.

6.2 Dose Finding and Dose Recommendation

Dose finding was initially based on investigations about reductions in the absolute peripheral lymphocyte count (ALC) in the phase 1 study 102. Daily intake of 10 mg ponesimod was associated with 30% ALC reduction vs. baseline and 40 mg ponesimod multiple dose with 70% ALC reduction. Roughly, 30% reduction in lymphocyte count has been considered to be the minimum required for an immunomodulatory effect, 70% reduction in ALC has been shown to be associated with a significant therapeutic effect in MS with the nonselective S1P receptor modulator fingolimod. With 20 mg ponesimod, a 50% ALC reduction was targeted for a meaningful therapeutic effect. Based on these considerations, 10, 20 and 40 mg ponesimod once daily were chosen for the dose-ranging study B201.
In the double-blind placebo-controlled phase 2 study B201 over 24 weeks, 464 patients with RRMS were randomised 1:1:1:1 to the treatment groups 10, 20 and 40 mg ponesimod and placebo. The initial dose was 10 mg in all active treatment groups. The dose was increased on day 8 to 20 mg in the 20 and 40 mg groups, and to 40 mg on day 15 in the 40 mg group. All three dose groups showed a statistically significant decrease in the cumulative number of new Gd+ T1 lesions over weeks 12,

16, 20, and 24 compared to placebo. Effects were dose-dependent for most of the endpoints from 10 mg to 20 mg ponesimod. The 40 mg dose showed further advantages over the 20 mg dose in the annual relapse rate (ARR) and the time to confirmed relapse, but not in Gd+ T1 lesions, cumulative number of new/enlarging T2 lesions or the cumulative number of combined unique active lesions (CUAL).
Results of the dose-finding study, as well as the results of the exploratory analysis of the ongoing long-term phase 2 extension study B202 (pooled B201/B202), showed that the 40 mg dose level was associated with higher rates of discontinuation, mainly due to increased pulmonary effects and associated adverse events (dyspnoea, cough, peripheral oedema). Therefore, the 40 mg dose was discontinued due to safety issues. In addition, the 10 mg dose was subsequently discontinued due to suboptimal efficacy, and the 20 mg dose was chosen for the pivotal study B301.
Two up-titration schemes for ponesimod were investigated in the phase 1 study 115, with a gradual titration approach of “regimen A” over 2 weeks starting with 2 mg/d up to 20 mg/d on day 15, compared to “regimen B”, starting with 10 mg and 1 single 20 mg dose in week 2. Heart rate decreases with regimen B (mean hourly heart rate decrease from baseline of 12 bpm and 13 beats per minute (bpm) as assessed by Holter ECG) were greater than with regimen A (6 bpm and 9 bpm) and placebo (0 bpm and 4 bpm). Also, the total number of occurrences of any AV block was largest during regimen B (143), followed by regimen A (79) and placebo (33). The company therefore chose to use the gradual up-titration regimen in the pivotal study B301.
The chosen 20 mg ponesimod for maintenance treatment as well as the up-titration regimen are considered as adequate, and this regimen is now recommended in the Swiss information for healthcare professionals.

6.3 Efficacy

Study design
Efficacy was evaluated in one pivotal multicentre, randomised, double-blind, active-controlled superiority phase 3 study (B301) to compare the efficacy and safety of 20 mg daily ponesimod to 14 mg daily teriflunomide. The treatment period was 108 weeks, which included an up-titration period of 14 days. After the randomised study period, there was a post-treatment period of 30 days for safety follow-up. The study included patients with MS with relapsing course from onset (RRMS, or SPMS with superimposed relapses), with confirmed disease activity. Disease activity was defined as one or more relapses with onset within the period of 12 to 1 months prior to baseline, or two or more relapses with onset within the period of 24 to 1 months prior to baseline assessment, or who had one or more Gd+ lesions prior to the baseline Expanded Disability Status Scale (EDSS) assessment.
The primary endpoint was the annual relapse rate (ARR). Secondary endpoints included the change in fatigue-related symptoms as measured by the symptom domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS), the cumulative number of combined unique active lesions (CUALs), the time to 12-week confirmed disability accumulation (CDA), and time to 24-week CDA.

Study population
Overall, 1468 subjects were screened, and 1133 subjects randomised in the full analysis set (567 to ponesimod 20 mg and 566 to teriflunomide 14 mg) at 162 centres in 28 countries. Treatment and study discontinuations were balanced across the two treatment groups, with 83% of subjects completing treatment (83.1% ponesimod 20 mg, 83.6% teriflunomide 14 mg). Main reasons for premature discontinuation in the ponesimod group were safety/tolerability issues, while discontinuations due to efficacy were more frequent in the teriflunomide group. The study population was predominantly white (97%), and 65% of subjects were female. The median age was 37 years with a range from 18 to 55 years. The mean BMI at baseline was 25 kg/m^2. Most of the subjects were enrolled at centres in Europe, with 51% from EU countries plus UK and 42% from non-EU European countries plus Russia (the majority of patients recruited in the EU came from eastern European countries).The study population predominantly included RRMS subjects (97.4%), while only n= 29 subjects (2.6%) had been diagnosed with SPMS. Mean time since first MS symptoms to

randomisation in the study was 7.6 years. The mean baseline EDSS score (electronic case report form eCRF data) was 2.6, with 84% of subjects having a baseline EDSS score ≤3.5. The mean pre-study 12- and 24-month relapse rates were 1.3 and 1.7 relapses, respectively. The proportion of subjects with at least 1 Gd+ T1 lesion at baseline was 42.6% (40% on ponesimod 20 mg, 45% on teriflunomide 14 mg). The proportion of treatment-naïve patients was 57%. Approximately 35% of subjects were considered to have highly active disease at baseline. The baseline disease characteristics in the Full Analysis Set (FAS) were generally balanced across the two treatment groups. A high rate (47%) of protocol deviations (PD), including important deviations like unblinding, was noted for this study. With the responses to Swissmedic`s List of Questions (LoQ), analyses were submitted excluding patients with important PDs and with adverse events (AEs) that potentially led to unblinding; results were still similar to the primary analysis. In addition, regarding patients from eastern EU countries, no differences in previous DMT were documented. The companies' responses regarding the validity of the trial were regarded as sufficient.

Efficacy results

For the primary endpoint, ponesimod 20 mg demonstrated a statistically significantly reduced ARR (confirmed relapses) up to End Of Study (EOS) by 30.5% compared to teriflunomide 14 mg (ARRs: 0.20 under ponesimod vs. 0.29 under teriflunomide, ratio: 0.695, CIs: 0.536, 0.902; p=0.0003). Several sensitivity analyses and missing data imputation scenarios supported the primary analysis. For most subpopulations, an effect similar to the overall primary outcome was noted. No difference in effects was seen between patients with any prior DMT vs. patients without prior DMT.

For the MRI-based secondary endpoints, clear advantages for ponesimod vs. teriflunomide were shown. For combined unique active lesions (CUAL), a rate ratio of 0.44 in favour of ponesimod was documented, and similar effects were seen for Gd+ T1 lesions and also for new or enlarging T2 lesions. Only small, numerical and statistically non-significant effects in favour of ponesimod could be shown for the secondary endpoints of time to 12-week confirmed disability accumulation (CDA) and time to 24-week CDA, which might be explained by the relatively short duration of the controlled study phase of 24 months, the choice of an active comparator or a slow progression of disability in the enrolled patient population.

A statistically significant difference was shown for time to first relapse, with around 40% patients with relapses under teriflunomide vs. 30% under ponesimod. The Kaplan Meier curves crossed at around 20 weeks suggesting a delayed effect of ponesimod vs. teriflunomide.

Another secondary endpoint, the FSIQ-RMS, had been newly developed as a patient-reported outcome and measure for MS-related fatigue. The result after 108 weeks showed a statistically significant mean difference of -3.57 points for ponesimod vs. the active comparator, although the clinical meaningfulness of these results remains unclear.

An increasingly important outcome in MS treatment is "no evidence of disease activity" (NEDA). With 15% patients under ponesimod vs. 8.5% patients under teriflunomide achieving NEDA-4 at week 108, the odds ratio (OR) was 1.85 in favour of ponesimod compared to teriflunomide, which can be regarded as a relevant effect. A slightly smaller effect was shown in the NEDA-3 analysis (OR 1.7, 28.2% under ponesimod vs. 18.3% under teriflunomide with NEDA-3 status at 108 weeks).

NEDA-3 was defined as absence of confirmed relapse, Gd+ lesions, new or enlarging T2 lesions, and 12-week CDA from baseline up to the specified time point. NEDA-4 adds no brain volume change.

Study B301 was followed by the ongoing open-label study B303. The sponsor provided an interim analysis with N=877 enrolled patients (cut-off date of 30 May 2019). The ARR observed in the ponesimod group in the pivotal study B301 remained stable during the extension study B302 (0.22, 95% CI 0.19, 0.25 in the combined analysis set).

For further details, please see the "Properties/effects" and the "Clinical efficacy" sections of the information for healthcare professionals.

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6.4 Safety

Exposure
By the cut-off dates of the different studies, 2205 subjects had been exposed to ponesimod. This includes 1438 subjects exposed to ponesimod monotherapy in the MS clinical programme, with long-term safety information from more than 200 MS subjects for up to 9 years of continuous treatment. In the phase 3 programme, 1003 subjects with RMS were exposed to ponesimod; 565 subjects were exposed to ponesimod 20 mg for up to 2 years in the pivotal monotherapy phase 3 study B301, and 877 subjects were exposed to ponesimod in the long-term extension phase 3 open-label monotherapy study B303, with 438 subjects newly exposed to ponesimod following previous teriflunomide 14 mg treatment in the pivotal phase 3 study B301. The safety database on ponesimod can be considered as sufficient for the evaluation of safety.

Adverse events
Consistent with what has been observed with other S1P receptor modulators, cardiac effects like conduction delay with bradycardia and AV blocks (predominantly during day 1, also with the first 2 mg dose in B301), hepatic enzyme elevations, pulmonary effects like dyspnoea and decreases in forced expiratory volume in 1 second (FEV1), infections, lymphopenia, macular oedema, skin malignancies and hypertension were documented with higher frequencies under ponesimod vs. placebo (in study B201) or vs. the active comparator teriflunomide (in study B301). Events with dose dependency were bradyarrhythmia, FEV1 reductions, absolute peripheral lymphocyte count (ALC) reductions and partly liver enzyme increases, especially pronounced in association with the 40 mg dose of ponesimod, which was abandoned in the later stages of the extension studies.
In general, the incidence of treatment-emergent adverse events (TEAEs) was similar between the ponesimod 20 mg and teriflunomide 14 mg in study B301, and most of them were mild or moderate in intensity. The most frequently reported TEAEs in study B301 were nasopharyngitis (19% under ponesimod vs. 17% under teriflunomide), headache (12% vs. 13%), upper respiratory tract infection (11% vs. 10%), hypertension (8% vs. 8%), nausea (8% vs .8%), fatigue (6% vs. 7%), back pain (6% vs. 7%), urinary tract infection (6% vs. 5%), ALT increased (20% vs. 9%), AST increased (6% vs. 4%), dyspnoea (5% vs. 1%), depression (4% vs. 5%), diarrhoea (4% vs. 8%) and alopecia (3% vs 13%).

Serious adverse events (SAEs) and deaths
In the active-controlled study B301, the incidences of SAEs were similar (8.7% vs. 8.1%) in the ponesimod 20 mg and teriflunomide 14 mg groups. SAEs reported in >1 subject were abdominal pain, appendicitis, induced abortion, and lumbar radiculopathy in the ponesimod 20 mg group, and cholelithiasis, increased ALT, concussion, metrorrhagia, and uterine leiomyoma in the teriflunomide 14 mg group. A total of three deaths were reported in the phase 2 and 3 MS studies (1 subject treated with ponesimod), and two additional deaths occurred in non-MS studies. Three subjects were treated with ponesimod. The causes of death were sudden cardiac death (2 subjects) and hepatic failure (1 subject).

Safety topics of special interest
The overall rate of **infections** was comparable between subjects receiving ponesimod 20 mg and those receiving teriflunomide 14 mg (54% vs. 52%, respectively) in the pivotal Phase 3 study B301. Nasopharyngitis and viral infections were more common in ponesimod 20 mg-treated subjects. Serious or severe infections occurred at a rate of 1.6% in ponesimod 20 mg-treated subjects compared to 0.9% of subjects receiving teriflunomide 14 mg. No cases of fatal infections, progressive multifocal leukoencephalopathy (PML), posterior reversible encephalopathy syndrome (PRES) or cryptococcal meningitis have been reported in ponesimod-treated subjects. No clear dose-dependency had been reported for infections in the dose-finding study B201.
In the phase 2 study B201 using the up-titration regimen with a starting dose of 10 mg, initiation of ponesimod treatment was associated with a number of clinically significant events of **bradycardia and second degree AV blocks**. The gradual up-titration regimen starting with ponesimod 2 mg in the

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phase 3 studies reduced the frequency of symptomatic bradycardia and high degree AV blocks. Maximum mean reduction in heart rate from pre- to post-dose on day 1 was observed at 2 hours post-dose in the ponesimod 20 mg group (-8.7 bpm) compared to -1.7 bpm in the teriflunomide 14 mg group in study B301.
In study B301, at treatment initiation, sinus bradycardia on ECG (HR <50 bpm) was observed in 5.8% of subjects in the ponesimod 20 mg group versus 1.6% in the teriflunomide 14 mg group; first degree AV block was observed in 3.4% of subjects in the ponesimod 20 mg group versus 1.2% in the teriflunomide 14 mg group. On day 1, in the subset of ponesimod 20 mg-treated subjects at risk for symptomatic bradyarrhythmia at baseline (definition: baseline heart rate < 55 beats per minute, PR interval > 200 msec, 2nd degree AV block, or a cardiac disorder reported at any time), the proportion of subjects with a new ECG finding of sinus bradycardia (HR <50 bpm) was 20%, compared to 3% (all asymptomatic) in the subset of subjects not at risk for symptomatic bradyarrhythmia. Three subjects at risk for symptomatic bradyarrhythmia in the ponesimod 20 mg group (with HR<55 bpm prior to ponesimod treatment initiation) experienced asymptomatic post-first-dose HR ≤40 bpm compared to none in the subset of subjects not at risk for symptomatic bradyarrhythmia. With the recommended up-titration regimen and the precautionary measures, the cardiac safety profile is improved to a certain extent.
Ponesimod was associated with an increased risk of **macular oedema**. In MS and plaque psoriasis clinical studies, confirmed events of macular oedema were reported at a rate of 0.7% (13 of 1742 subjects). Most cases (77%) occurred within the first 6 months of therapy. In Study B301, macular oedema was reported in 1.1% (6 of 565 subjects) of ponesimod-treated subjects compared to none receiving teriflunomide. In these cases, macular oedema was reversible (resolved upon ponesimod treatment discontinuation).
Dose-dependent **reductions in FEV1 and reductions in DLCO** (diffusion lung capacity for carbon monoxide, assessed only in the ponesimod 20 mg groups) were observed in ponesimod-treated subjects, mostly occurring in the first month after treatment initiation. Incidences of pulmonary AEs at different dose levels indicated that the effect of ponesimod on pulmonary function was similar at ponesimod 10 mg and 20 mg dose levels, but clearly stronger at the 40 mg dose level. In study B301, the percent reduction from baseline in %predFEV1 at 2 years was 8.3% in ponesimod 20 mg-treated subjects compared to 4.4% in subjects receiving teriflunomide 14 mg. Changes in FEV1 and DLCO were only partially reversible after treatment discontinuation, meaning that mean FEV1 and DLCO reductions did not return to baseline values. Seven (1.2%) subjects discontinued ponesimod because of pulmonary AEs. Ponesimod has also been tested in MS subjects with mild to moderate pre-existing lung disorders (e.g. asthma or chronic obstructive pulmonary disease). The changes in %predFEV1 were similar in this subgroup compared to the subgroup of subjects without baseline lung disorders. At the concentrations expected after 20 mg once daily dosing, the model-predicted net FEV1 reduction was about 5%.
Elevations **of ALT and/or AST** have been observed during ponesimod treatment. In Study B301, ALT increased to 3 and 5×ULN (upper limit of normal) in 17.3% and 4.6% of ponesimod 20 mg-treated subjects, respectively, compared to 8.3% and 2.5% of subjects, respectively, receiving teriflunomide 14 mg. ALT increased to 8×ULN in 0.7% ponesimod 20 mg-treated subjects, compared to 2.1% in subjects receiving teriflunomide 14 mg. The majority of elevations occurred within 6 or 12 months of starting treatment. There were two cases that met the Hy's law criteria in the ponesimod clinical programme, but these were confounded by other medical conditions. While most cases of ALT increase ≥3×ULN were single transient asymptomatic episodes that resolved on continued ponesimod treatment, the company should adapt the SmPC with additional precautionary measures (liver function tests, consistent with the SmPC for other approved S1P modulators).
In Study B301, cases of **seizures** were reported in 1.4% (n = 8) of ponesimod 20 mg-treated subjects, compared to 0.2% (n = 1) of subjects receiving teriflunomide 14 mg. Higher frequencies of seizures have been observed also with other S1P modulators (siponimod, fingolimod).
In the complete (long-term) safety data pool, no cases of posterior reversible encephalopathy syndrome (**PRES**), progressive multifocal leukoencephalopathy (**PML**), cryptococcal meningitis, other opportunistic infections with fatal outcome or reversible cerebral vasoconstriction syndrome were reported during ponesimod treatment.

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A total of 11 (out of 1438) ponesimod-treated subjects in the MS programme reported a **skin malignancy** AE. In Study B301, a higher proportion of subjects (n = 5, 0.9%) in the ponesimod 20 mg group compared to one (0.2%) subject in the teriflunomide 14 mg group had an AE of skin malignancy. Basal cell carcinoma was reported in two (0.4%) ponesimod-treated subjects compared to one (0.2%) subject receiving teriflunomide. A case of malignant melanoma was reported in the ponesimod 20 mg group. A total of 10 ponesimod-treated subjects in the MS programme reported a **non-skin malignancy.** The only AE that was reported in more than 1 subject in the ponesimod 20 mg group was invasive ductal breast carcinoma (3 subjects, 0.3%).

For further details, please see the “Undesirable effects” and the “Warnings and precautions” sections of the information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Introduction
Ponesimod is an orally active, potent selective modulator of S1P1 that induces a rapid (within hours of dosing), and dose-dependent reduction in peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. The effect is reversible within 1 week after stopping treatment. The recommended dose of ponesimod is 20 mg once daily taken orally with an initial dose escalation regimen from Days 1-14, starting with 2 mg ponesimod daily.
The clinical programme of ponesimod for treatment of MS included several phase 1 PK and phase 2 PD-studies, one phase 2, randomised, double-blind, placebo-controlled dose-finding study over 6 months (B201) with a blinded extension period (B202), one double-blind, active-controlled (teriflunomide) pivotal phase 3 study over 24 months (B301) and one open-label long-term extension study (B303). Interim reports are available for the two extension studies B202 and B303. With responses to LoQ, an updated safety report for the extension studies B202 and B303 was submitted (data cut-off March 2020). Meanwhile, Ponvory has been approved in the US (18 March 2021), Canada (18 April 2021) and the EU (19 May 2021).

Beneficial Effects
Clinical Pharmacology
The oral bioavailability of ponesimod is high. There was no evidence of nonlinear pharmacokinetics in the investigated dose range. Fed administration had no effect on ponesimod absorption.
From a pharmacokinetic point of view, no dose adjustments were required for patients with mild hepatic impairment, renal impairment of all degrees, age, gender, or body weight.
The pharmacokinetic interaction potential as victim or perpetrator appeared to be low.
At therapeutic exposures, a QTc prolongation appeared to be unlikely.
Clinical Aspects
In the dose-finding study B201, superior efficacy was demonstrated for 10, 20 and 40 mg ponesimod in MRI measures of MS disease activity and some clinical measures, mostly with signs of dose response. The 40 mg dose level was associated with higher rates of discontinuation, mainly due to increased pulmonary effects like dyspnoea, cough and peripheral oedema, which is why the 40 mg dose was abandoned. The 20 mg dose was chosen for the pivotal study B301 due to better efficacy compared to the 10 mg dose.
Superior efficacy for 20 mg ponesimod in clinical and MRI measures of MS disease activity was demonstrated in the pivotal study B301 vs. the active comparator teriflunomide (14 mg). The effect in ARR was around a 30% risk reduction, which can be regarded as clinically relevant when using an established active comparator. The times to 12 weeks-CDA and 24 weeks-CDA were not statistically significant for 20 mg ponesimod, which might be explained by the relatively short duration of the controlled study phase of 24 months and the choice of an active comparator.

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Uncertainties regarding the Beneficial Effects

Clinical Pharmacology

No PK data in end-stage renal disease (ESRD) patients on dialysis were available. The therapeutic dose of 20 mg QD was not investigated in the tQT study.

Clinical Aspects

The requested indication “treatment of RMS” requires an adequate proportion of patients with SPMS. In the pivotal study B301, n = 15 (2.6%) patients with SPMS and superimposed relapses were treated with ponesimod, and no effect was shown in this small subpopulation. Since these sparse data are not regarded as a sufficient basis for an RMS indication, the indication wording targets patients with RRMS.

Although clinical efficacy data are available from B201 and B301, there is only one controlled pivotal phase 3 trial over a sufficient time span of 24 months. The validity of this single pivotal trial was the subject of questions to the company, since a high number of protocol deviations (PD) were observed, and unblinding due to AEs was a potential issue. With the responses to LoQ, analyses were submitted excluding patients with important PDs and with AEs that potentially led to unblinding; results were still similar to the primary analysis. In addition, regarding patients from eastern EU countries, no differences in previous DMT were documented. Overall, the responses regarding the validity of the trial can be regarded as sufficient.

Another secondary endpoint, the FSIQ-RMS, had been newly developed as a patient-reported outcome and measure for MS-related fatigue. The result after 108 weeks showed a statistically significant mean difference of -3.57 points for ponesimod vs. the active comparator. However, the clinical meaningfulness remained unproven (validation, effect size), and therefore the results are not presented in the SmPC.

Unfavourable Effects

Clinical Pharmacology

There was substantial evidence of unidentified, possibly active, ponesimod metabolites in plasma. It has not been possible so far to identify the enzymes involved in the formation of M13 (the known “main metabolite” in plasma).

Ponesimod is contraindicated in patients with moderate or severe hepatic impairment. Ponesimod caused a pronounced bradycardia at treatment start, which required a long, slow up-titration of the dose. This is a class effect. However, compared to other S1P1 receptor modulators, ponesimod seemed to be more potent in this respect. There was a remarkable number of drop-outs due to cardiovascular AEs in the Phase 1 studies in healthy subjects. One pharmacodynamic interaction study was terminated due to cardiovascular SAEs. The required up-titration period is twice as long as for other S1P1 modulators

Ponesimod caused a concentration-dependent QTc prolongation at supratherapeutic exposures. Ponesimod had a considerable pharmacodynamic interaction potential with other compounds causing bradycardia, like beta blockers or calcium channel blockers.

Clinical Aspects

Ponesimod caused cardiac effects like bradycardia, AV blocks (including higher degrees), hepatic enzyme elevations, pulmonary effects like dyspnoea and FEV1-decreases that were not fully reversible, infections, lymphopenia, macular oedema, skin malignancies and hypertension in higher frequencies compared to placebo or the active comparator teriflunomide.

Overall, ponesimod showed a safety profile that did not exhibit completely new aspects compared to the three already approved S1P-modulators fingolimod, siponimod and ozanimod. For some adverse effects like bradycardia/conduction delay or pulmonary effects, it was unclear if they could be more pronounced under ponesimod compared to other S1P modulators. The company responded with additional analyses and explanations, which support the position that these effects are comparable to the other S1P modulators. The question if active but yet unidentified metabolites could play a role for safety issues was not clearly answered, but was not regarded as prohibitive for approval. The SmPC was adapted in some sections (e.g. “contraindications”) for consistency with the SmPCs for other S1P modulators.

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Uncertainties regarding the Unfavourable Effects
Clinic
Long -term data are still limited, especially when considering possible development of malignancies that have been documented in higher frequencies under ponesimod, which could be even more pronounced in treatments over many years.

Benefit-Risk Conclusions
Conclusions: Clinical Pharmacology:
The main issues from a clinical pharmacology point of view were the insufficient metabolite identification and the considerable pharmacodynamic interaction potential with other compounds causing bradycardia. The latter was managed by appropriate labelling. As most other S1P1 receptor modulators have slowly formed metabolites with long half-lives and variable pharmacological activity, the insufficient metabolite identification for ponesimod could present a problem.
Conclusions: Clinical Assessment:
Ponesimod is an orally active, selective modulator of S1P1 that induces a rapid (within hours of dosing) and dose-dependent reduction in peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. The effect is reversible within 1 week after stopping treatment.
Superior efficacy for 20 mg ponesimod in the clinical measure ARR and several MRI measures of multiple sclerosis disease activity was demonstrated in a single, but adequately designed, pivotal study B301 over 108 weeks of double-blind treatment vs. the active comparator teriflunomide (14 mg). The reduction of the ARR was around 30%, which can be regarded as clinically relevant. No significant advantage for ponesimod vs. teriflunomide was shown in disability progression. The sparse data for patients with SPMS (2.6% of the study population) were regarded as not sufficient for a broad RMS indication, which is why the indication wording targets patients with RRMS.
As compared to the three already approved S1P-modulators, no new safety signals emerged. Cardiac effects like conduction delay with bradycardia and AV-blocks, hepatic enzyme elevations, pulmonary effects like dyspnoea and FEV1-decreases, infections, lymphopenia, macular oedema, skin malignancies and hypertension have been documented with higher frequencies under ponesimod. With the proposed up-titration schedule during the first 14 days of treatment and other precautionary measures included in the information for healthcare professionals, most of these risks can be adequately mitigated.
Based on the currently available data, the ratio of benefits and risks for ponesimod is regarded as favourable in the indication "*Ponvory is indicated for the treatment of adult patients with relapsing remitting forms of multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features"*.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ponvory, film-coated tablets, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "*Undesirable effects*" section for advice on the reporting of adverse reactions.

Ponvory

Composition

Active substances

Ponesimod.

Excipients

Tablet core: Croscarmellose sodium*, lactose monohydrate**, magnesium stearate, microcrystalline cellulose, povidone K30, colloidal anhydrous silica, sodium laurilsulfate*.
Tablet coating: Hypromellose/Hydroxypropylmethylcellulose 2910, Lactose monohydrate**, Macrogol / Polyethylene glycol 3350, Titanium dioxide, Triacetin, Iron oxide red (E172) included in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg and 10 mg film-coated tablets, Ferrosoferric oxide / Black iron oxide (E172) included in 4 mg, 5 mg, 8 mg and 9 mg film-coated tablets, Iron oxide yellow (E172) included in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg and 20 mg film-coated tablets.
* Ponvory contains up to 1.80 mg sodium.
** Ponvory contains up to 124.60 mg lactose monohydrate.

Pharmaceutical form and active substance quantity per unit

Film-coated tables
Ponvory 2 mg film-coated tablets contain 2 mg ponesimod (round, biconvex, white, 5.0 mm tablet size, debossed with "2" on one side and an arch on the other side)
Ponvory 3 mg film-coated tablets contain 3 mg ponesimod (round, biconvex, red, 5.0 mm tablet size, debossed with "3" on one side and an arch on the other side)
Ponvory 4 mg film-coated tablets contain 4 mg ponesimod (round, biconvex, purple, 5.0 mm tablet size, debossed with "4" on one side and an arch on the other side)
Ponvory 5 mg film-coated tablets contain 5 mg ponesimod (round, biconvex, green, 8.6 mm tablet size, debossed with "5" on one side and an arch and an "A" on the other side)

Ponvory 6 mg film-coated tablets contain 6 mg ponesimod (round, biconvex, white, 8.6 mm tablet size, debossed with "6" on one side and an arch and an "A" on the other side)
Ponvory 7 mg film-coated tablet contains 7 mg ponesimod (round, biconvex, red, 8.6 mm tablet size, debossed with "7" on one side and an arch and an "A" on the other side)
Ponvory 8 mg film-coated tablets contain 8 mg ponesimod (round, biconvex, Purple, 8.6 mm tablet size, debossed with "8" on one side and an arch and an "A" on the other side)
Ponvory 9 mg film-coated tablets contain 9 mg ponesimod (round, biconvex, brown, 8.6 mm tablet size, debossed with "9" on one side and an arch and an "A" on the other side)
Ponvory 10 mg film-coated tablets contain 10 mg ponesimod (round, biconvex, orange, 8.6 mm tablet size, debossed with "10" on one side and an arch and an "A" on the other side)
Ponvory 20 mg film-coated tablets contain 20 mg ponesimod (round, biconvex, yellow, 8.6 mm tablet size, debossed with "20" on one side and an arch and an "A" on the other side)

Indications/Uses

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

Dosage/Administration

Assessments prior to first dose of Ponvory

Before initiation of treatment with Ponvory, assess the following:
Complete blood count
Review results of a complete blood count (CBC) with differential White Blood Cell (WBC) count obtained within the last 6 months (see *Warnings and Precautions*).
Liver function tests
Review results of transaminase and bilirubin levels obtained within the last 6 months (see *Warnings and Precautions*).
Pregnancy test
Before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available (see *Pregnancy, lactation*).
Ophthalmic evaluation
Obtain an evaluation of the fundus, including the macula (see *Warnings and Precautions*).
Cardiac evaluation
Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist and first-dose monitoring is recommended (see *Dosage/Administration*, *First dose monitoring in patients with certain pre-existing cardiac conditions* and *Warnings and Precautions*).
Determine whether patients are taking medicinal products that could slow heart rate or atrioventricular (AV) conduction (see *Interactions*).

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 immunosuppressive effects before initiating treatment with Ponvory (see *Warnings and Precautions* and *Interactions*).

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating Ponvory; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Ponvory (see *Warnings and Precautions*).

Initiation of treatment

A starter pack must be used for patients initiating treatment with Ponvory (see *Packs*). Initiate Ponvory treatment with a 14-day titration; start with one 2 mg tablet orally once daily and progress with the titration schedule outlined in Table 1 (see *Warnings and Precautions*).

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 *Delayed administration* below).

Maintenance therapy

After dose titration is complete (see *Treatment Initiation* above), the recommended maintenance dosage of Ponvory is one 20 mg tablet taken orally once daily.

Special dosage instructions

Patients with impaired hepatic function

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) (see *Pharmacokinetics*).
Based on clinical pharmacology studies in adult subjects with moderate or severe hepatic impairment, ponesimod $AUC_{0-\infty}$ was increased 2.0- and 3.1-fold respectively, compared to healthy subjects. Ponvory is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively)(see *Contraindication*).

Patients with impaired renal function

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

Elderly patients

Ponvory has not been studied in patients 65 years of age and older. Clinical trials in MS included patients up to 55 years of age. In elderly patients, Ponvory should be used with caution due to the lack of sufficient data on safety and efficacy.

Children and adolescents

The safety and efficacy of Ponvory have not been established in pediatric patients aged 18 years and younger. No data is available.

Delayed administration

Interruption during treatment, especially during titration, should be avoided, however:

- if less than 4 consecutive doses are missed, resume treatment with the first missed dose.
- if 4 or more consecutive doses are missed, reinitiate treatment with Day 1 of the titration regimen (new starter pack).

During treatment initiation or maintenance, if treatment needs to be reinitiated with Day 1 of the titration regimen, complete first-dose monitoring in patients for whom it is recommended (see Warnings and Precautions).

Mode of administration

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

Contraindications

Ponvory is contraindicated:

- in patients who have known hypersensitivity to the active substance or an excipient contained according to its composition.
- in patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure.
- in patients who have presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (see *Warnings and Precaution*).
- in patients who have moderate or severe hepatic impairment (Child-Pugh class B and C, respectively).
- in patients who have an immunodeficient state (see Warnings and Precautions).
- in patients who have severe active infections or active chronic infections.
- in patients who have active malignancies.
- during pregnancy and in women of childbearing potential not using reliable contraception (see *Pregnancy, lactation*).

Warnings and precautions

Bradyarrhythmia and atrioventricular conduction delays

Initiation of treatment with Ponvory

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 Ponvory treatment may result in a transient decrease in heart rate (HR) and AV conduction delays (see *Undesirable effects* and *Clinical efficacy*), therefore an up titration scheme must be used to reach the maintenance dose of Ponvory (20 mg) (see *Dosage/Administration*).

After the first dose of Ponvory, 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 was 6 beats per minute (bpm). With up titration after day 1, the decrease in HR is less pronounced.

Caution should be applied when Ponvory is initiated in patients receiving treatment with a beta blocker because of the additive effects on lowering heart rate; temporary interruption of the beta blocker treatment may be needed prior to initiation of Ponvory (see below and *Interactions*).

For patients receiving a stable dose of a beta blocker, the resting HR should be considered before introducing Ponvory treatment. If the resting HR is greater than 55 bpm under chronic beta blocker treatment, Ponvory 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 Ponvory can then be initiated and treatment with a beta-blocker can be reinitiated after Ponvory has been up titrated to the target maintenance dose (see *Interactions*). Beta blocker treatment can be initiated in patients receiving stable doses of Ponvory.

First dose monitoring in patients with certain pre existing cardiac conditions
Because initiation of Ponvory treatment may result in a decrease in HR, first-dose 4 hour monitoring is recommended for patients with sinus bradycardia [HR less than 55 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 *Pharmacodynamics*).

First dose 4 hour monitoring
Administer the first dose of Ponvory in a setting where resources to appropriately manage symptomatic bradycardia are available. Monitor patients for 4 hours after the first dose for signs and symptoms of bradycardia with a minimum of hourly pulse and blood pressure measurements. Obtain an ECG in these patients at the end of the 4-hour observation period.

Additional monitoring after 4 hour monitoring
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 Ponvory 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 *Interaction*)

- 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 *Contraindication*)
- In patients with a history of recurrent syncope or symptomatic bradycardia
- In patients receiving concurrent therapy with drugs that decrease heart rate (eg, beta-blockers, non dihydropyridine calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease HR such as digoxin) (see above and *Interactions*), consider potential 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.

Infections

Risk of infections

Ponvory causes a dose-dependent reduction in peripheral lymphocyte count to 30-40% of baseline values due to reversible sequestration of lymphocytes in lymphoid tissues. Ponvory may therefore increase the risk of infections (see *Undesirable effects*). No cases of fatal infections have been reported in Ponvory-treated patients in the development program, however, life-threatening and rare fatal infections have been reported in association with other sphingosine 1-phosphate (S1P) receptor modulators.

Before initiating treatment with Ponvory, results from a recent complete blood count with differential (including lymphocyte count) (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

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

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

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

Herpes viral infections

Cases of herpes viral infection have been reported in the development program of Ponvory (see *Undesirable effects*).

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 Ponvory. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Ponvory. Delay treatment with Ponvory for 4 weeks after vaccination to allow the full effect of vaccination to occur (see *Vaccinations* below).

Cryptococcal infections

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with other S1P receptor modulators. No cases of CM have been reported in Ponvory -treated patients in the development program. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. Ponvory treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in Ponvory-treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with Ponvory should be suspended until PML has been excluded.

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 Ponvory (see *Interactions*).
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 Ponvory.
Pharmacokinetic/pharmacodynamic modeling indicates lymphocyte counts returned to the normal range in >90% of healthy subjects within 1 week of stopping Ponvory therapy (see *Pharmacodynamics*). In the development program, pharmacodynamic effects, such as lowering of peripheral lymphocyte counts, were restored to normal within 1 week after the last dose.
Use of immunosuppressants may lead to an additive effect on the immune system, and therefore caution should be applied up to 1 week after the last dose of Ponvory (*see Interactions*).

Vaccinations
No clinical data are available on the efficacy and safety of vaccinations in patients taking Ponvory. Vaccinations may be less effective if administered during Ponvory treatment. Avoid the use of live attenuated vaccines while patients are taking Ponvory. If the use of live attenuated vaccine immunization is required, Ponvory treatment should be paused from 1 week prior to 4 weeks after a planned vaccination (see *Interactions*).

Macular edema
Ponvory increases the risk of macular edema (see *Undesirable effects*). An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and again at any time if a patient reports any change in vision while on Ponvory therapy.
In the clinical trial experience in patients with all doses of ponesimod, the rate of macular edema was 0.7%. Most cases occurred within the first 6 months of therapy.
Continuation of Ponvory therapy in patients with macular edema has not been evaluated. A decision on whether Ponvory should be discontinued should take into account the potential benefits and risks for the individual patient.

Macular edema 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 edema during therapy with S1P receptor modulators. Therefore, these patients should have regular follow-up examinations of the fundus, including the macula, during treatment with Ponvory.

Respiratory effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and reductions in diffusion lung capacity for carbon monoxide (DL_{CO}) were observed in Ponvory-treated patients mostly occurring in the first month after treatment initiation (see *Undesirable effects*). Respiratory functional impairement was not completely reversible in every case in the clinical trial. Respiratory symptoms associated with Ponvory treatment can be reversed with administration of a short-acting $beta_2$ agonist. Ponvory should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Spirometric evaluation of respiratory function should be performed during therapy with Ponvory if clinically indicated.

Liver injury

Elevations of transaminases may occur in Ponvory-treated patients (see *Undesirable effects*). Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of Ponvory 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. Ponvory should be discontinued if significant liver injury is confirmed.

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 Ponvory, caution should be exercised when using Ponvory in patients with a history of significant liver disease (see *Contraindications*).

Increased blood pressure

A mild reversible increase in blood pressure (mean change less than 3.0 mmHg) was observed in patients treated with Ponvory (see *Undesirable effects*). Blood pressure should be monitored during treatment with Ponvory and managed appropriately.

Fetal risk

Based on animal studies, Ponvory may cause fetal harm. Due to the risk to the fetus, Ponvory is contraindicated during pregnancy and in women of childbearing potential not using reliable contraception (see *Contraindications* and *Pregnancy, lactation*). Because it takes approximately 1 week to eliminate Ponvory from the body, women of childbearing potential should use reliable contraception to avoid pregnancy during and for 1 week after stopping Ponvory treatment.

Posterior reversible encephalopathy syndrome

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

neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral 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 ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, Ponvory should be discontinued.

Severe exacerbation of disease after stopping Ponvory
Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping Ponvory treatment. Patients should be observed for a severe increase in disability upon Ponvory discontinuation and appropriate treatment should be instituted, as required.

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Ponvory contains less than 1 mmol sodium (23 mg) per 1 tablet, i.e. it is almost "sodium-free".

Interactions

Anti-neoplastic, immune-modulating, or immunosuppressive therapies
Ponvory has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration (see *Warnings and Precautions*).

Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate
Ponvory has not been studied in patients taking QT prolonging drugs (see *Warnings and Precautions*).

Beta-blockers
The negative chronotropic effect of co-administration of Ponvory and propranolol was evaluated in a dedicated pharmacodynamics safety study. The addition of Ponvory to propranolol at steady state has an additive effect on HR (see *Interactions*).

In a drug-drug interaction study, the up-titration regimen of ponesimod (see *Dosage/Administration*) was administered to subjects receiving propranolol (80 mg) once daily at steady-state. No significant changes in pharmacokinetics of ponesimod or propranolol were observed. Compared to ponesimod alone, the combination with propranolol after the first dose of ponesimod (2 mg) had a 12.4 bpm (90%

CI: -15.6 to -9.1) decrease in mean hourly heart rate and at the first dose of ponesimod (20 mg) after up-titration a 7.4 bpm (90% CI: -10.9 to -3.9) decrease in mean hourly heart rate.

Vaccines

Vaccinations may be less effective if administered while being treated with Ponvory and up to 1 week after its discontinuation (*see Warnings and Precautions*).

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

Effect of Ponvory on other medicinal products

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. However, based on in vitro data, inhibition of BCRP by ponesimod cannot be excluded at an intestinal level. Therefore, increased exposure may occur for medicinal products transported by BCRP. This interaction has not been investigated in clinical trials and thus caution should be used in the co-administration of ponesimod and drugs that are transported by BCRP.

Oral contraceptives

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

Effect of other medicinal products on Ponvory

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

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

Co-administration of Ponvory with strong inducers of several enzymes involved in the metabolism of ponesimod may decrease the systemic exposure of ponesimod. It is unclear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance.

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

Pregnancy, lactation

Women of childbearing potential/Contraception in females

Ponvory is contraindicated in women of childbearing potential not using reliable contraception (see *Contraindications*). Before initiation of Ponvory treatment in women of childbearing potential, a negative pregnancy test result must be available, and women should be counseled on the potential for a serious risk to the fetus and the need for reliable contraception during treatment with Ponvory (see *Pregnancy* below). Since it takes approximately 1 week to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women must use reliable contraception during this period (see *Warnings and Precaution*s).

Pregnancy

Ponvory is contraindicated during pregnancy (see *Contraindications*). If a woman becomes pregnant during treatment, Ponvory must be immediately discontinued.
Based on human experience in patients receiving another S1P receptor modulator, post-marketing data suggest that its use is associated with an increased risk of major congenital malformations.
There are no adequate and well-controlled studies of Ponvory in pregnant women. Animal studies showed embryotoxicity and fetotoxicity in rats and rabbits and teratogenic effects in rats (see *Preclinical data*).

Lactation

There are no data on the presence of Ponvory or its metabolites in human milk. A study in lactating rats has shown excretion of ponesimod in milk (see Preclinical data).
A risk to newborns/infants cannot be excluded. Ponvory should not be used while breastfeeding.

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 *Preclinical data*).

Effects on ability to drive and use machines

Ponvory has no or negligible influence on the ability to drive and use machines. However, no studies on the ability to drive or use machines have been performed. Symptomatic bradyarrhythmias may occasionally occur when initiating therapy with Ponvory. Therefore, patients should not drive or use machines during the first day of treatment initiation with Ponvory.

Undesirable effects

Summary of the safety profile

A total of 1438 MS patients have received Ponvory at doses of at least 2 mg daily. These patients were included in the Phase 3 study OPTIMUM (2-year active-controlled versus teriflunomide 14 mg)

study (*see Clinical efficacy*) and in a Phase 2 (6-month placebo-controlled) study in patients with MS and their uncontrolled extension studies.

Tabulated list of adverse reactions

Adverse reactions reported with Ponvory 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).

Infections and infestations

Very common: Nasopharyngitis (19.7%), upper respiratory tract infection (11%).

Common: 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

Common: Lymphopenia, lymphocyte count decreased.

Psychiatric disorders

Common: Depression, insomnia, anxiety.

Nervous system disorders

Common: Dizziness, hypoesthesia, somnolence, migraine.

Eye disorders

Common: Macular oedema.

Ear and labyrinth disorders

Common: Vertigo.

Cardiac disorders:

Uncommon: Bradycardia.

Vascular disorders

Common: Hypertension.

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea, cough.

Gastrointestinal disorders

Common: Dyspepsia.

Uncommon: Dry mouth.

Musculoskeletal and connective tissue disorders

Common: Back pain, arthralgia, pain in extremity, ligament sprain.

Uncommon: Joint swelling.

General disorders and administration site conditions

Common: Fatigue, pyrexia, oedema peripheral, chest discomfort.

Investigations

Very common: Alanine aminotransferase increased (17.9%).

Common: Aspartate aminotransferase increased, hypercholesterolaemia, hepatic enzyme increased, c-reactive protein increased, transaminases increased, blood cholesterol increased.

Uncommon: Hyperkalaemia.

Description of selected undesirable effects

Bradyarrhythmia atrioventricular conduction delays

In Phase 3 study OPTIMUM (see *Pharmacodynamics*), bradycardia at treatment initiation (sinus bradycardia/HR less than 50 bpm on ECG on day 1) occurred in 5.8% of Ponvory-treated patients compared to 1.6% of patients receiving teriflunomide 14 mg. Patients who experienced bradycardia were generally asymptomatic. Bradycardia resolved without intervention and did not require discontinuation of Ponvory treatment. On Day 1, 3 patients treated with Ponvory had asymptomatic post dose HR below or equal to 40 bpm; all 3 patients had baseline HRs below 55 bpm.

Initiation of Ponvory treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested as first-degree AV block (prolonged PR interval on ECG), which occurred in 3.4% of Ponvory -treated patients and in 1.2% of patients receiving teriflunomide 14 mg in the phase 3 study OPTIMUM. No second degree AV blocks, Mobitz type I (Wenckebach), were observed in phase 3 study OPTIMUM. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, resolved without intervention, and did not require discontinuation of Ponvory treatment.

Infections

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

In the phase 3 study OPTIMUM, the rate of herpetic infections was not different between the Ponvory-treated patients and those receiving teriflunomide 14 mg (4.8%).

Macular oedema

In the phase 3 study OPTIMUM, macular oedema was reported in 1.1% of Ponvory-treated patients compared to none of the patients receiving teriflunomide 14 mg.

Liver enzymes elevation

In the phase 3 study OPTIMUM study, ALT increased to three and five times the upper limit of normal (ULN) in 17.3% and 4.6% of Ponvory-treated patients, respectively, compared to 8.3% and 2.5% of patients receiving, teriflunomide 14 mg, respectively. ALT increased eight times ULN in 0.7% Ponvory-treated patients compared to 2.1% in patients receiving teriflunomide 14 mg. The majority of elevations occurred within 6 or 12 months of starting treatment. ALT levels returned to normal after discontinuation of Ponvory. Most cases of ALT increases ≥3×ULN resolved on continued Ponvory treatment, and the remaining cases resolved upon treatment discontinuation. In clinical trials, Ponvory was discontinued if the elevation exceeded a 3 fold increase and the patient showed symptoms related to hepatic dysfunction.

Seizures

In the phase 3 study OPTIMUM, cases of seizures were reported in 1.4% of Ponvory-treated patients, compared to 0.2% in patients receiving teriflunomide 14 mg. It is not known whether these events were related to the effects of MS, to Ponvory, or to a combination of both.

Respiratory effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) were observed in patients treated with Ponvory (see *Warnings and Precautions*). In the phase 3 study OPTIMUM, the reduction from baseline in percent predicted FEV_1 at 2 years was 8.3% in Ponvory-treated patients compared to 4.4% in patients receiving teriflunomide 14 mg. The changes in FEV_1 and DL_{CO} appear to be partially reversible after treatment discontinuation. In the phase 3 study OPTIMUM study, 7 patients discontinued Ponvory because of pulmonary adverse events. Ponvory has been tested in MS patients with mild to moderate asthma or chronic obstructive pulmonary disease. The changes in FEV_1 were similar in this subgroup compared with the subgroup of patients without baseline lung disorders.

Increased blood pressure

In the phase 3 study OPTIMUM, Ponvory-treated patients had an average increase of 2.9 mmHg in systolic blood pressure and 2.8 mmHg in diastolic blood pressure compared to 2.8 mmHg and 3.1 mmHg in patients receiving teriflunomide 14 mg, respectively. An increase in blood pressure with Ponvory was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. The blood pressure values after Ponvory treatment discontinuation indicate reversibility.

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

Malignancies

In the phase 3 study OPTIMUM, a case of malignant melanoma and two cases of basal cell carcinoma (0.4%) were reported in Ponvory-treated patients compared to one case of basal cell carcinoma (0.2%) in patients receiving teriflunomide 14 mg. An increased risk of cutaneous malignancies has been reported in association with another S1P receptor modulator. Physicians and patients should remain alert for the potential development of skin malignancies. Patients should be informed against exposure to sunlight without protection and avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

In patients with overdosage of Ponvory, especially upon initiation/re-initiation of treatment, it is important to observe for signs and symptoms of bradycardia as well as AV conduction blocks, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed (see *Warnings and Precautions* and *Pharmacodynamics*).

Treatment

There is no specific antidote to ponesimod. Neither dialysis nor plasma exchange would result in meaningful removal of ponesimod from the body. The decrease in heart rate induced by Ponvory can be reversed by atropine.
In the event of overdose, Ponvory should be discontinued, and general supportive treatment given until clinical toxicity has been diminished or resolved. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

Properties/Effects

ATC code

L04AA50

Mechanism of action

Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator. Ponesimod binds with high affinity to S1P receptor 1 located on lymphocytes.
Ponesimod blocks the capacity of lymphocytes to egress from lymph nodes reducing the number of lymphocytes in peripheral blood. The mechanism by which ponesimod exerts therapeutic effects in multiple sclerosis may involve reduction of lymphocyte migration into the central nervous system.

Pharmacodynamics

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. PK/PD modeling indicates lymphocyte counts returned to the normal range in >90% of healthy subjects within 1 week of stopping therapy. In the development program, peripheral lymphocyte counts returned to the normal range within 1 week after discontinuation of Ponvory.

Heart rate and rhythm

Ponesimod causes a transient dose dependent reduction in heart rate (HR) and AV conduction delays upon treatment initiation (see *Warnings and Precautions*). The heart rate decreases plateaued at doses greater than or equal to 40 mg, and bradyarrhythmic events (AV blocks) were detected at a higher incidence under Ponvory treatment, compared to placebo. This effect starts within the first hour of dosing and is maximal at 2-4 hours post-dose and HR generally returns to pre-dose values by 4-5 hours post-dose on Day 1 and the effect diminishes with repeated administration, indicating tolerance. With the gradual up-titration of ponesimod, the HR reduction is less pronounced and no second-degree AV blocks of Mobitz type II or higher degree were observed.

The decrease in heart rate induced by ponesimod can be reversed by atropine.

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 prolongation of individually corrected QT (QTcI) interval, with the upper bound of 90% two-sided confidence interval (CI) at 11.3 ms (40 mg) and 14.0 ms (100 mg). There was no consistent signal of increased incidence of QTcI outliers associated with ponesimod treatment, either as absolute values or change from baseline. Based on the concentration-effect relationship, no clinically relevant effect on QTc interval is expected for the therapeutic dose of 20 mg.

Pulmonary function

Dose-dependent reductions in absolute forced expiratory volume over 1 second were observed in ponesimod-treated subjects and were greater than in subjects taking placebo (see *Warnings and Precautions* and *Undesirable effects*)

Clinical efficacy

The efficacy of Ponvory was demonstrated in the phase 3 study, OPTIMUM, a multicentre, randomized, 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 randomized to receive either once daily Ponvory or teriflunomide 14 mg, beginning with a 14-day dose titration (see *Dosage/Administration*). 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 annualized relapse rate (ARR) from baseline up to end of study (EOS). The prespecified hierarchical fallback testing sequence included the primary endpoint and following 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 the phase 3 study OPTIMUM, 1133 patients were randomized to either Ponvory (N=567) or teriflunomide 14 mg (N=566); 86.4% of Ponvory-treated patients and 87.5% of teriflunomide 14 mg-treated patients completed the study as per protocol. The baseline demographic and disease characteristics were balanced between the treatment groups. At baseline, the mean age of patients was 37 years, 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 for MS. At baseline, 40% of Ponvory-treated patients had one or more Gd+ T1 lesions on brain MRI (mean 1.9).

Results are presented in Table 2. Analysis of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of Ponvory on the primary and secondary endpoints was consistent with the overall population.

Table 2: Efficacy Results of phase 3 study OPTIMUM

	20 mg Ponvory	**Teriflunomide 14 mg**
Clinical Endpoint	N=567	N=566
Mean Annualized Relapse Rate[a]	0.202	0.290
Relative ARR reduction	30.5% (p=0.0003)[*]	
Patients with at least one confirmed relapse	29.3%	39.4%

MRI Endpoints		
Cumulative number of Combined Unique Active Lesions (CUALs)	N=539	N=536
Mean number of CUALs per year[b]	1.41	3.16
Relative reduction	56% (p<0.0001)*	
Brain volume	N=436	N=434
Mean % change from Baseline to Week 108 in brain volume	-0.91%	-1.25%
Mean difference	0.34% (p<0.0001)*	
Confirmed Disability Accumulation (CDA) up to Week 108[c]	N=567	N=566
Patients[c] with first 12-week CDA	10.8%	13.2%
Relative risk reduction[d]	17% (p = NS)	
Patients[c] with first 24-week CDA	8.7%	10.5%
Relative risk reduction[d]	16% (p = NS)	

[a] Defined as confirmed relapses per year up to EOS
[b] Defined as new Gd+ T1 lesions plus new or enlarging T2 lesions per year from baseline to Week 108
[c] Based on time to first 12-Week/24-Week CDA event up to Week 108 (Kaplan-Meier estimates)
[d] 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]).
* statistically significant (p<0.05), NS: not statistically significant, treatment comparisons: Relative rate/risk (Ponvory vs Teriflunomide 14 mg,) and Mean difference (Ponvory - Teriflunomide 14 mg).

Pharmacokinetics

The pharmacokinetic profile of ponesimod is characterized by low inter-subject variability, approximately 25% across studies.
The pharmacokinetics of ponesimod is similar in healthy subjects and subjects with multiple sclerosis.

Absorption

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

Food effect

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

Distribution

Following IV administration in healthy subjects, the steady-state volume of distribution of ponesimod is 160 L.
Ponesimod is highly bound to plasma proteins, (> 99%) and is mainly (78.5%) distributed in the plasma fraction of whole blood. Animal studies show that ponesimod readily crosses the blood-brain-barrier.

Metabolism

Ponesimod is extensively metabolized 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.

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 feces (16% as unchanged ponesimod), and 10% to18% in urine (no unchanged ponesimod).
Linearity/non-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.
Kinetics in specific patient groups

Hepatic impairment

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

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 PK of ponesimod has not been studied. Due to the high plasma protein binding (greater than 99%) of ponesimod, dialysis is not expected to alter the total and unbound ponesimod concentration and no dose adjustments are anticipated based on these considerations

Elderly patients

The results from population pharmacokinetics of ponesimod demonstrated age (range: 17 to 65 years) was not identified to significantly influence the PK 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 subjects.

Preclinical data

Safety Pharmacology / Long-term toxicity

The preclinical safety profile of ponesimod has been evaluated in safety pharmacology studies that have identified the respiratory system and heart as target organs, as well as single and multiple dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks) and dogs (up to 52 weeks). Dose-limiting/adverse toxicities in animal species were liver effects in mice, effects on weight gain in rats, and adverse CNS, skin and cardiovascular effects in dogs. Organs identified by histopathology and most affected by toxic effects included the lung (mouse, rat, dog), heart (dog), skin (dog) and adrenals (rat). In the lung, transient adaptive pulmonary histiocytosis and lung weight increase were observed in mice, rats, and dogs after subacute treatment with ponesimod, but were no longer present or were less pronounced after prolonged treatment. These findings are considered secondary to increased vascular permeability caused by $S1P_1$ receptor modulation. The no-observed-adverse-effect levels (NOAELs) for lung findings were identified in rat and dog 4-week toxicity studies and were associated with C_{max} and AUC_{0-24} values similar or inferior to human total and peak systemic exposures following RHD of 20 mg/day.

In the heart of the dog, arterial lesions were observed in the posterior papillary muscles of the left ventricle, secondary to hemodynamic changes, after 13, 26, and 52 weeks of treatment at ≥5 mg/kg/day. The dog is known to be particularly sensitive to hemodynamic changes in the heart and the associated toxicity. When compared with human systemic exposures at RHD of 20 mg/day the NOAEL in the dog was 4.3 and 6.2 times the human systemic exposures based on $AUC_{0–24}$ and C_{max}, respectively.

Mutagenicity

Ponesimod was negative in a number of *in vitro* tests (Ames test, mammalian cell chromosome aberration test) and *in vivo* tests (rat micronucleus test).

Carcinogenicity

Oral carcinogenicity studies of ponesimod were conducted in mice and rats. In rats, ponesimod was administered at oral doses of 3, 10 and 30 mg/kg/day in males and 100 mg/kg/day in females for up to 2 years. Ponesimod did not induce neoplastic lesions. The highest doses tested (30/100 mg/kg/day) are 3.6 and 18.7 times the human systemic exposures at RHD of 20 mg based on the steady state clinical AUC_{0-24}.

In mice, ponesimod was administered at oral doses of 50, 150 and 400 mg/kg/day in males and 30, 100 and 300 mg/kg/day in females for up to 2 years. In mice, ponesimod increased the combined total incidence of hemangiosarcoma and hemangioma in all treated males and high dose level females. The lowest dose tested in females is considered as 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. These tumor findings were considered to be mouse specific. The clinical relevance for humans is not known.

Reproductive toxicity

In the male and female fertility studies in rats, mating and fertility were unaffected by treatment at doses up to 100 mg/kg/day. There was no effect on early pregnancy and no effect on sperm parameters. Plasma exposure (AUC) at the NOAEL in the rat was approximately 18 and 31 times (for males and females, respectively) that in humans at the RHD of 20 mg/day.

No effects were observed on male reproductive organs when evaluated histopathologically in repeat dose toxicology studies for up to 26 or 52 weeks in rats or dogs, respectively.

When ponesimod was orally administered (1, 10, 40 mg/kg/day) to pregnant rats during the period of organogenesis, embryo-fetal survival, growth, and morphological development were severely compromised at 40 mg/kg/day. Teratogenic effects with major skeletal and visceral abnormalities were observed at doses $\geq$ 10 mg/kg/day. A NOAEL for embryo-fetal developmental toxicity in rats was established at 1 mg/kg/day. When ponesimod was orally administered (0.25, 1, 4 mg/kg/day) to pregnant rabbits during the period of organogenesis, a slight increase in post-implantation losses and fetal findings (visceral and skeletal) were noted at 4 mg/kg/day. The embryo-fetal NOAEL in rabbits was 1 mg/kg/day. The AUC_{0-24} in rats and rabbits at the NOAEL (1 mg/kg/day in both species) are lower than the human systemic exposures at the RHD of 20 mg/day.

When ponesimod was orally administered (5, 10, or 20 mg/kg) to female rats throughout pregnancy and lactation, decreased pup survival and body weight gain, and reduced fertility (females only) were observed in the offspring at 20 mg/kg only. All ponesimod treated F1 pups had delayed sexual maturation. The AUC_{0-24} at the NOAEL of 10 mg/kg/day is 1.2 to 1.5 times that in humans at the RHD

of 20 mg/day. Ponesimod was present in the plasma of F1 pups, indicating exposure from the milk of the lactating dam.

Phototoxicity

Ponesimod showed no potential to induce phototoxicity in cultured mammalian cells.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep the container in the outer carton in order to protect the contents from moisture.
Keep out of the reach of children.

Authorisation number

68114 (Swissmedic).

Packs

High-density polyethylene (HDPE) blister consists of a laminated Alu cold form film with integrated desiccant and a laminated Alu push-through lidding film.

Starter pack

Each Ponvory carton (blister pack) of 14 film-coated tablets contains:
2 film-coated tablets of 2 mg ponesimod
2 film-coated tablets of 3 mg ponesimod
2 film-coated tablets of 4 mg ponesimod
1 film-coated tablet of 5 mg ponesimod
1 film-coated tablet of 6 mg ponesimod
1 film-coated tablet of 7 mg ponesimod
1 film-coated tablet of 8 mg ponesimod
1 film-coated tablet of 9 mg ponesimod
3 film-coated tablets of 10 mg ponesimod

Ponvory 20 mg carton: 28 film-coated tablets (maintenance pack).

Marketing authorisation holder

Janssen-Cilag AG, Zug, Zug.

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