NDA 213498/S-01

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Tania Hillmer, MS, RAC
Associate Director, Global Regulatory Affairs-Neuroscience
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560

Dear Ms. Hillmer:

Please refer to your supplemental new drug application (sNDA) dated and received April 30, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ponvory (ponesimod) tablets, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg.

This "Changes Being Effected" sNDA provides for editorial revisions in the Highlights of Prescribing Information (Contraindications, Bullet 2) and Patient Counseling Information (Section 17, Risk of Infections) to align with text in the Contraindications and Warnings and Precautions sections of the Full Prescribing Information.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. If the content of labeling in SPL format initially submitted with this CBE-0 labeling supplement is identical to the attached approved labeling, an additional submission of content of labeling in SPL format is not required.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kristen Haslam, Senior Regulatory Project Manager, at (240)-402-4246.

Sincerely,

{See appended electronic signature page}

Alice T.D. Hughes, MD
Deputy Director of Safety
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Study 1): rhinitis, fatigue, chest discomfort, peripheral edema, joint swelling, blood cholesterol increased, migraine, insomnia, depression, dyspepsia, dry mouth, bradycardia, back pain, and sinusitis.

Additionally, in uncontrolled extension trials, the adverse reaction of pneumonia was reported.

Seizures

In Study 1, 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

In Study 1, dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) were observed in patients treated with PONVORY *[see Warnings and Precautions (5.3)]*.

Malignancies

In Study 1, 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, and a case of malignant melanoma was reported in a PONVORY-treated patient. An increased risk of cutaneous malignancies has been reported in association with other S1P receptor modulators, including PONVORY *[see Warnings and Precautions (5.6)]*.

7 DRUG INTERACTIONS

7.1 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 (5.1)]*.

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive effects on the immune system *[see Warnings and Precautions (5.10)]*.

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with PONVORY after alemtuzumab is not recommended.

PONVORY can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs that may Decrease Heart Rate

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

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with PONVORY is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with PONVORY should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., digoxin) *[see Warnings and Precautions (5.2) and Drug Interactions (7.3)]*. If treatment with PONVORY is considered, advice from a cardiologist should be sought.

7.3 Beta-Blockers

Caution should be applied when PONVORY is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of PONVORY *[see Warnings and Precautions (5.2)]*. Beta-blocker treatment can be initiated in patients receiving stable doses of PONVORY.

7.4 Vaccination

During, and for up to 1 to 2 weeks after discontinuation of, treatment with PONVORY, vaccinations may be less effective. The use of live *attenuated* vaccines may carry the risk of infection and should therefore be avoided during PONVORY treatment and for 1 to 2 weeks after discontinuation of treatment with PONVORY *[see Warnings and Precautions (5.1)]*.

7.5 Strong CYP3A4 and UGT1A1 Inducers

In vitro assessments and limited clinical data indicated that concomitant use of strong CYP3A4 and UGT1A1 inducers (e.g., rifampin, phenytoin, carbamazepine) may decrease the systemic exposure of ponesimod. It is unclear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance. Coadministration of PONVORY with strong CYP3A4 and UGT1A1 inducers is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of PONVORY in pregnant women. In animal studies, administration of ponesimod during pregnancy produced adverse effects on development, including embryo lethality and fetal malformations, in the absence of maternal toxicity. In rats and rabbits, visceral and skeletal malformations occurred at clinically relevant maternal ponesimod exposures *(see Data)*. The receptor affected by ponesimod (sphingosine-1-phosphate receptor 1) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When ponesimod (0, 1, 10, or 40 mg/kg/day) was orally administered to pregnant rats during the period of organogenesis, increased incidences of fetal malformations primarily involving the limbs (syndactyly and ectrodactyly) and cardiovascular system (including ventricular septal defects) were observed at all but the lowest dose tested. A high incidence of embryofetal death was observed at the highest dose tested. Maternal toxicity was not observed, indicating a selective effect on the fetus. Plasma exposure (AUC) at the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development in rats was lower than that in humans at the recommended human dose (RHD) of 20 mg/day.

When ponesimod (0, 0.25, 1, or 4 mg/kg/day) was orally administered to pregnant rabbits during the period of organogenesis, an increase in post-implantation loss and fetal variations (visceral and skeletal) were noted at the highest dose tested. No maternal toxicity was observed. Plasma exposure at the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development in rabbits was lower than that in humans at the RHD. In a dose-range finding study in pregnant rabbits, oral administration of ponesimod (0, 6, 20, or 60 mg/kg/day) during organogenesis, an increase in embryofetal death and fetal limb malformation (brachydactyly) were observed at the lowest dose tested; at the higher doses, there were no live fetuses.

When ponesimod (5, 10, or 20 mg/kg) was orally administered to female rats throughout pregnancy and lactation, the offspring exhibited decreased survival, reduced body weight gain, and reduced fertility and reproductive performance (increases in pre- and post-implantation loss) at the highest dose tested, neurobehavioral impairment (increased locomotor activity) at the mid and high doses, and delayed sexual maturation at all doses tested. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. Plasma exposure (AUC) in dams at the lowest dose tested was less than that in humans at the RHD.

8.2 Lactation

Risk Summary

There are no data on the presence of PONVORY in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. When ponesimod was orally administered to female rats during pregnancy and lactation, ponesimod was detected in the plasma of the offspring, suggesting excretion of ponesimod in milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PONVORY and any potential adverse effects on the breastfed infant from PONVORY or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Before initiation of PONVORY treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with PONVORY *[see Use in Specific Populations (8.1)]*. Since it takes approximately one week to eliminate ponesimod from the body after stopping treatment, the potential risk to the fetus may persist, and women should use effective contraception during this period *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Oral administration of ponesimod (0, 1, 10, 30, or 100 mg/kg/day) to young rats from postnatal day 28 to 91 resulted in lung histopathology (alveolar histiocytosis/edema) and decreased immune function (T-cell dependent antibody response) at the two highest doses tested. Decreased growth (body weight gain and/or long bone length) was observed at all but the low dose, and neurobehavioral impairment (increased locomotor activity) was observed at the highest dose tested. Decreased lymphocyte count and neurobehavioral impairment persisted at the end of a 4-week recovery period.

8.5 Geriatric Use

Clinical studies of PONVORY did not include patients 65 years of age and over to determine whether they respond differently from younger subjects. Use of PONVORY in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A) *[see Clinical Pharmacology (12.3)]*.

PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C, respectively), as the risk of adverse reactions may be greater *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Symptoms and Signs

In patients with overdosage of PONVORY, especially upon initiation/reinitiation 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 (5.2, 5.5) and Clinical Pharmacology (12.2)]*.

Treatment

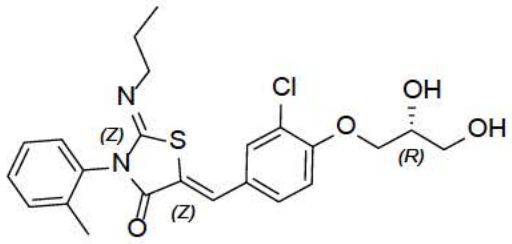
There is no specific antidote to ponesimod. Neither dialysis nor plasma exchange would result in meaningful removal of ponesimod from the body. The decrease in heart rate induced by PONVORY can be reversed by atropine.

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.

11 DESCRIPTION

PONVORY (ponesimod) is a sphingosine 1-phosphate receptor modulator.

The chemical name for ponesimod is (2*Z*,5*Z*)-5-[3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]benzylidene]-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one. It has one chiral center with absolute configuration of *(R)*. Its molecular formula is $C_{23}H_{25}ClN_2O_4S$ and its molecular weight is 460.97 g/mol. Ponesimod has the following structural formula:



Ponesimod is a white to light yellowish powder that is practically insoluble or insoluble in water.

PONVORY (ponesimod) is provided as 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg film-coated tablets for oral administration.

Each tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, silica colloidal anhydrous, and sodium lauryl sulfate.

Each tablet coating contains ferrosoferric oxide (included in 4 mg, 5 mg, 8 mg, and 9 mg film-coated tablets), hydroxypropyl methylcellulose 2910, iron oxide red (included in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg, and 10 mg film-coated tablets), iron oxide yellow (included in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg, and 20 mg film-coated tablets), lactose monohydrate, polyethylene glycol 3350, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator that binds with high affinity to S1P receptor 1.

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 is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

12.2 Pharmacodynamics

Immune System

In healthy volunteers, PONVORY induces a dose-dependent reduction of the peripheral blood lymphocyte count from a single dose of 5 mg onwards, with the greatest reduction observed 6 hours post-dose, caused by reversible sequestration of lymphocytes in lymphoid tissues. After 7 daily doses of 20 mg, the greatest decrease in absolute mean lymphocyte count was to 26% of baseline (650 cells/µL), observed 6 hours after administration. Peripheral blood B cells [CD19+] and T cells [CD3+], T-helper [CD3+CD4+], and T-cytotoxic [CD3+CD8+] cell subsets are all affected, while NK cells are not. T-helper cells were more sensitive to the effects of ponesimod than T-cytotoxic cells.

PK/PD modeling indicates lymphocyte counts returned to the normal range in greater than 90% of healthy subjects within 1 to 2 weeks of stopping therapy. In Study 1, peripheral lymphocyte counts returned to the normal range within 2 weeks after discontinuation of PONVORY.

Heart Rate and Rhythm

PONVORY causes a transient dose-dependent reduction in heart rate (HR) and AV conduction delays upon treatment initiation *[see Warnings and Precautions (5.2)]*. The heart rate decreases plateaued at doses greater than or equal to 40 mg [2 times the recommended maintenance dosage], 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. 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.

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

Beta-Blockers

The negative chronotropic effect of coadministration 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 effect *[see Drug Interactions (7.3)]*.

Cardiac Electrophysiology

In a thorough QT study, daily administration of ponesimod doses of 40 mg and 100 mg (respectively 2- and 5-fold the recommended maintenance dose) until steady-state conditions were achieved resulted in prolongation of Fridericia-corrected QT (QTcF) intervals, with the maximum mean (upper bound of 90% two-sided confidence interval) at 11.8 ms (40 mg) and 16.2 ms (100 mg). No subject had absolute QTcF greater than 480 ms or ΔQTcF greater than 90 ms for ponesimod treatment.

Pulmonary Function

Dose-dependent reductions in FEV_1 and FVC were observed in PONVORY-treated subjects, and were greater than in subjects taking placebo *[see Warnings and Precautions (5.3)]*. These effects can be reversed with administration of a short acting beta2 agonist.

12.3 Pharmacokinetics

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 3 days of administration of the maintenance dose of ponesimod.

The pharmacokinetics of ponesimod are similar in healthy subjects and patients with multiple sclerosis, with 25% inter-subject variability across studies.

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 84%.

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 and M12 are respectively about

20% and 6% of total drug-related exposure. Both metabolites are inactive at S1P receptors at concentrations achieved with recommended doses of ponesimod.

Experiments with human liver preparations indicate that metabolism of ponesimod to M13 occurs primarily through a combination of non-Cytochrome P450 (CYP450) enzymatic activities. Multiple CYP450 (CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12) and non-CYP450 enzymes catalyze the oxidation of ponesimod to M12. Ponesimod also undergoes direct glucuronidation (mainly UGT1A1 and UGT2B7).

Excretion

After a single IV administration, the total clearance of ponesimod is 3.8 L/hour. The elimination half-life after oral administration is approximately 33 hours.

Following a single oral administration of ^{14}C-ponesimod, 57% to 80% of the dose was recovered in feces (16% as unchanged ponesimod), and 10% to 18% in urine (no unchanged ponesimod).

Specific Populations

Renal Impairment

No dose adjustment is necessary in patients with renal impairment. In adult subjects with moderate or severe renal impairment (estimated creatinine clearance [CrCl], as determined by the Cockroft-Gault, between 30-59 mL/min for moderate and <30 mL/min for severe), there were no significant changes in ponesimod C_{max} and AUC, compared to subjects with normal renal function (CrCl>90 mL/min). The effect of dialysis on the PK of ponesimod has not been studied. Due to the high plasma protein binding (greater than 99%) of ponesimod, dialysis is not expected to alter the total and unbound ponesimod concentration, and no dose adjustments are anticipated based on these considerations.

Hepatic Impairment

In adult subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B and C, respectively), no change in ponesimod C_{max} was observed, but ponesimod $AUC_{0-\infty}$ was increased by 1.3-, 2.0-, and 3.1-fold, respectively, compared to healthy subjects *[see Use in Specific Populations (8.6)]*.

Age

Age (range: 17 to 65 years) was not identified to significantly influence the PK of ponesimod in population pharmacokinetics analyses. The effect of age (65 years of age and older) on the pharmacokinetics of ponesimod is unknown *[see Use in Specific Populations (8.5)]*.

Gender

Gender has no clinically significant influence on ponesimod pharmacokinetics.

Race

No clinically relevant pharmacokinetic differences were observed between Japanese and Caucasian subjects.

Drug Interaction Studies

Beta-Blockers

In a drug-drug interaction study, the dose titration regimen of ponesimod *[see Dosage and Administration (2.2)]* 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 of propranolol and the first dose of ponesimod (2 mg) led to a mean hourly heart rate decrease of 12.4 bpm (90% CI: -15.6 to -9.1). Compared to ponesimod alone, propranolol administered in combination with the first maintenance dose of ponesimod (20 mg) led to a 7.4 bpm (90% CI: -10.9 to -3.9) mean hourly heart rate decrease.

Effect of Other Drugs on 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.

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.

In vitro assessments and limited clinical data indicated that concomitant use of strong CYP3A4 and UGT1A1 inducers (e.g., rifampin, phenytoin, carbamazepine) may decrease the systemic exposure of ponesimod *[see Drug Interactions (7.5)]*.

Effect of Ponesimod on Other Drugs

In vitro investigations indicate that at the recommended 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.

Oral Contraceptives

Coadministration 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ponesimod to mice (0, 50, 150, or 400 mg/kg/day in males and 30, 100, or 300 mg/kg/day in females) for up to 2 years resulted in incidences in hemangiosarcoma and combined hemangioma and hemangiosarcoma in males at all doses and at the highest dose tested in females. Plasma exposure (AUC) at the lowest dose tested in males (50 mg/kg/day) was approximately 5 times that in humans at the recommended human dose (RHD) of 20 mg.

Oral administration of ponesimod to rats (0, 3, 10, or 30 mg/kg/day in males and 0, 10, 30 or 100 mg/kg/day in females) for up to 2 years did not result in an increase in tumors. Plasma exposure at the highest dose tested in males (30 mg/kg/day) was approximately 4 times that in humans at the recommended human dose (RHD) of 20 mg.

Mutagenesis

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

Fertility

In separate studies, oral administration of ponesimod (0, 10, 30, or 100 mg/kg/day) to male and female rats prior to and throughout the mating period and continuing in females to Day 6 of gestation resulted in no effects on fertility. Plasma ponesimod exposures (AUC) at the highest dose tested were approximately 10 (males) and 30 (females) times that in humans at the recommended human dose (RHD) of 20 mg/day.

13.2 Animal Toxicology and/or Pharmacology

Increases in lung weight and histopathology (alveolar histiocytosis, edema) were observed in oral toxicity studies in mice, rats, and dogs. At the higher doses tested in short-term studies, alveolar histiocytosis was associated with lung edema, emphysema, or hyalinosis, and with bronchioloalveolar hyperplasia after cessation of dosing in rats and alveolar histiocytosis and hyalinosis in dogs. Effects tended to be absent or less severe after chronic treatment. These findings are considered secondary to increased vascular permeability caused by $S1P_1$ receptor modulation. The NOAELs for lung findings in the 4-week oral toxicity studies in rats and dogs were associated with plasma exposures (AUC) similar or lower than that expected in humans at the recommended human dose (RHD) of 20 mg/day.

In dogs, coronary arterial lesions (thickening of the vessel wall, hyperplasia/hypertrophy of smooth muscles cells of the tunica media, subendocardial fibrosis) involving the papillary muscle of the left ventricle were observed in oral toxicity studies of 13 to 52 weeks in duration. At the NOAEL (2 mg/kg/day) for these findings, plasma exposures (AUC) were approximately 2 times that expected in humans at the RHD.

14 CLINICAL STUDIES

The efficacy of PONVORY was demonstrated in Study 1, a randomized, double-blind, parallel group, active-controlled superiority study in patients with relapsing forms of MS (NCT02425644). Patients were treated for 108 weeks. This study included patients who had an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at baseline, had experienced at least one relapse within the year prior, or two relapses within the prior 2 years, or who had at least one gadolinium-enhancing (Gd-enhancing) lesion on a brain MRI within the prior 6 months or at baseline. Patients with primary progressive MS were excluded.

Patients were randomized to receive either once daily PONVORY, beginning with a 14-day dose titration *[see Dosage and Administration (2.2)]* or teriflunomide 14 mg. Neurological evaluations were performed at baseline, every 3 months during the study, and at the time of a suspected relapse. Brain MRI scans were performed at baseline and at Weeks 60 and 108.

The primary endpoint was the annualized relapse rate (ARR) over the study period. Additional outcome measures included: 1) the number of new Gd-enhancing T1 lesions from baseline to Week 108, 2) the number of new or enlarging T2 lesions (without double-counting of lesions) from baseline to Week 108, and 3) the time to 3-month and 6-month confirmed disability progression. A confirmed disability progression was defined as an increase of at least 1.5 in EDSS for patients with a baseline EDSS score of 0, an increase of at least 1.0 in EDSS for patients with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for patients with a baseline EDSS score at least 5.5, which was confirmed after 3 months and 6 months.

A total of 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. 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 non-steroid treatments for MS. At baseline, 42.6% of patients had one or more Gd-enhancing T1 lesions (mean 2.0) on their baseline MRI scan.

The ARR was statistically significantly lower in patients treated with PONVORY than in patients who received teriflunomide 14 mg. The number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions were statistically significantly lower in patients treated with PONVORY than in patients who received teriflunomide 14 mg.

There was no statistically significant difference in the 3-month and 6-month confirmed disability progression outcomes between PONVORY- and teriflunomide 14 mg-treated patients over 108 weeks.

The efficacy results for Study 1 are presented in Table 4.

Table 4: Clinical and MRI Endpoints from Study 1

Endpoints	**PONVORY 20 mg** N =567	**Teriflunomide 14 mg** N =566
Clinical Endpoints		
Annualized Relapse Rate[a]	0.202	0.290
Relative reduction	30.5% (p=0.0003)	
Percentage of patients without relapse[b]	70.7%	60.6%
Proportion of Patients with 3-month Confirmed Disability Progression[c]	10.8%	13.2%
Hazard Ratio[d]	0.83 (p=0.29)[e]	
MRI Endpoints[b, f]		
Mean number of new or enlarging T2 hyperintense lesions per year	1.40	3.16
Relative reduction	55.7% (p <.0001)	
Mean number of T1 Gd-enhancing lesions per MRI	0.18	0.43
Relative reduction	58.5% (p <.0001)	

All analyses are based on the full analysis set (FAS), which includes all randomized patients. N refers to the number of patients included in the FAS, per treatment group.

[a] Defined as confirmed relapses per year through the study period (Negative binomial regression model with stratification variables (EDSS ≤ 3.5 versus EDSS > 3.5; non-steroid treatment for MS within last 2 years prior to randomization [Yes/No]) and the number of relapses in the year prior to study entry (<=1, >=2) as covariates)

[b] Over the study period of approximately 108 weeks

[c] Disability progression defined as 1 5-point increase in EDSS for patients with a baseline EDSS score of 0, 1.0-point increase in EDSS for patients with a baseline EDSS score of 1.0 to 5.0, or 0.5-point increase in EDSS for patients with a baseline EDSS score at least 5.5 confirmed 3 months later. Proportion of patients with 3-month confirmed disability progression refers to Kaplan-Meier estimates at Week 108.

[d] Defined as time to 3 months confirmed disability progression through the study period (Stratified Cox proportional hazard model, p-value based on the stratified log rank test)

[e] Not statistically significant

[f] Cumulative number of combined unique active lesions (CUALs), defined as new or enlarging T2 lesions or Gd-enhancing T1 lesions (without double counting), mean lesions per year were 1.41 on ponesimod 20 mg (N=539), and 3.16 on teriflunomide 14 mg (N=536), a relative reduction of 56% (p<0.0001).

A similar effect of PONVORY on the ARR and secondary MRI outcomes compared to teriflunomide 14 mg was observed in exploratory subgroups defined by age, gender, prior non-steroid therapy for MS, and baseline disease activity.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PONVORY™ (ponesimod) tablet is available as round, biconvex, film-coated tablets supplied in the following dosage strengths and package configurations.

Starter Pack

Tablet Strength	Tablet Color	Tablet Size	Tablet Debossing	Pack Size	NDC Code
2 mg	White	5.0 mm	"2" on one side and an arch on the other side.	Child Resistant Starter Pack (14 tablets)	NDC 50458-707-14
3 mg	Red	5.0 mm	"3" on one side and an arch on the other side.		
4 mg	Purple	5.0 mm	"4" on one side and an arch on the other side.		
5 mg	Green	8.6 mm	"5" on one side and an arch and an "A" on the other side.		
6 mg	White	8.6 mm	"6" on one side and an arch and an "A" on the other side.		
7 mg	Red	8.6 mm	"7" on one side and an arch and an "A" on the other side.		
8 mg	Purple	8.6 mm	"8" on one side and an arch and an "A" on the other side.		
9 mg	Brown	8.6 mm	"9" on one side and an arch and an "A" on the other side.		
10 mg	Orange	8.6 mm	"10" on one side and an arch and an "A" on the other side.		

Maintenance Dose Bottle

Tablet Strength	Tablet Color	Tablet Size	Tablet Debossing	Pack Size	NDC Code
20 mg	Yellow	8.6 mm	"20" on one side and an arch and an "A" on the other side.	Bottle of 30 tablets with child-resistant closure. Each bottle contains a desiccant sachet and a polyester coil.	NDC 50458-720-30

16.2 Storage and Handling

Starter Pack

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

Store in the original package.

Maintenance Dose Bottle

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

Store in the original package. Do not discard desiccant. Protect from moisture.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

Tell patients not to discontinue PONVORY without first discussing this with the prescribing healthcare provider. Advise patients to contact their healthcare provider if they accidently take more PONVORY than prescribed.

Instruct patients to administer tablets whole.

Risk of Infections

Inform patients that they may have an increased risk of infections, some of which could be life-threatening, when taking PONVORY and for 1 to 2 weeks after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection *[see Warnings and Precautions (5.1)]*. Advise patients that the use of some vaccines containing live virus (live *attenuated* vaccines) should be avoided during treatment with PONVORY, and PONVORY should be paused 1 to 2 weeks prior and until 4 weeks after a planned vaccination. Recommend that patients postpone treatment with PONVORY for at least 1 month after VZV vaccination. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection.

Cardiac Effects

Advise patients that initiation of PONVORY treatment results in transient decrease in heart rate *[see Warnings and Precautions (5.2)]*. Inform patients that to reduce this effect, dose titration is required. Advise patients that dose titration is also required if 4 or more consecutive daily doses are missed during treatment initiation or maintenance treatment *[see Dosage and Administration (2.2, 2.4) and Warnings and Precautions (5.2)]*. Inform certain patients with certain preexisting cardiac conditions that they will need to be observed in the doctor's office or other facility for at least 4 hours after the first dose and after reinitiation if treatment is interrupted or discontinued for certain periods *[see Dosage and Administration (2.3)]*.

Respiratory Effects

Advise patients that they should contact their healthcare provider if they experience new onset or worsening of dyspnea *[see Warnings and Precautions (5.3)]*.

Liver Injury

Inform patients that PONVORY may increase liver enzymes. Advise patient that they should contact their healthcare provider if they experience any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment *[see Warnings and Precautions (5.4)]*.

Cutaneous Malignancies

Inform patients that the risk of basal cell carcinoma is increased with the use of PONVORY and that cases of melanoma and squamous cell carcinoma have been reported. Advise patients that any suspicious skin lesions should be promptly evaluated. Advise patients to limit exposure to sunlight and ultraviolet light by wearing protective clothing and using a sunscreen with high protection factor *[see Warnings and Precautions (5.6)]*.

Pregnancy and Fetal Risk

Inform patients that, based on animal studies, PONVORY may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with PONVORY and for one week after stopping PONVORY. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant *[see Warnings and Precautions (5.7)]*.

Macular Edema

Advise patients that PONVORY may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision while taking PONVORY *[see Warnings and Precautions (5.8)]*. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema is increased.

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological sequelae *[see Warnings and Precautions (5.9)]*.

Severe Increase in Disability After Stopping PONVORY

Inform patients that severe increase in disability has been reported after discontinuation of another S1P receptor modulator like PONVORY. Advise patients to contact their healthcare provider if they develop worsening symptoms of MS following discontinuation of PONVORY *[see Warnings and Precautions (5.11)]*.

Immune System Effects After Stopping PONVORY

Advise patients that PONVORY continues to have effects, such as lowering effects on peripheral lymphocyte count, for 1 to 2 weeks after the last dose *[see Warnings and Precautions (5.12)]*.

Active ingredient made in Austria.

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

MEDICATION GUIDE
PONVORY™ (pon-VOR-ee)
(ponesimod)
tablets, for oral use

What is the most important information I should know about PONVORY?

PONVORY may cause serious side effects, including:

1. **Infections.** PONVORY can increase your risk of serious infections that can be life-threatening and cause death. PONVORY lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 1 to 2 weeks of stopping treatment. Your healthcare provider should review a recent blood test of your white blood cells before you start taking PONVORY.

   Call your healthcare provider right away if you have any of these symptoms of an infection during treatment with PONVORY and for 1 to 2 weeks after your last dose of PONVORY:

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

   Your healthcare provider may delay starting or may stop your PONVORY treatment if you have an infection.

2. **Slow heart rate (bradycardia or bradyarrhythmia) when you start taking PONVORY.** PONVORY can cause your heart rate to slow down, especially after you take your first dose. You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of PONVORY.

   Only start your treatment with PONVORY using the Starter Pack. You must use the PONVORY Starter Pack to slowly increase the dose over a 14-day period to help reduce the effect of slowing of your heart rate. It is important to follow the recommended dosing instructions. See "**How should I take PONVORY**?"

   Call your healthcare provider if you experience the following symptoms of slow heart rate:

   - dizziness
   - lightheadedness
   - feeling like your heart is beating slowly or skipping beats
   - shortness of breath
   - confusion
   - chest pain
   - tiredness

Follow directions from your healthcare provider when starting PONVORY and when you miss a dose. See **"How should I take PONVORY?"**

See "What are possible side effects of PONVORY?" for more information about side effects.

What is PONVORY?

- PONVORY is a prescription medicine that is used to treat relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- It is not known if PONVORY is safe and effective in children.

Do not take PONVORY if you:

- have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months.
- have certain types of heart block or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker.

Talk to your healthcare provider before taking PONVORY if you have any of these conditions, or do not know if you have any of these conditions.

Before you take PONVORY, tell your healthcare provider about all of your medical conditions, including if you:

- have a fever or infection, or you are unable to fight infections due to a disease or taking medicines that weaken your immune system.
- have had chicken pox or have received the vaccine for chicken pox. Your healthcare provider may do a blood test for chicken pox virus. You may need to get the full course of vaccine for chicken pox and then wait 1 month before you start taking PONVORY.
- have slow heart rate.
- have an irregular or abnormal heartbeat (arrhythmia).
- have a history of stroke.
- have heart problems, including a heart attack or chest pain.
- have breathing problems, including during your sleep (sleep apnea).
- have liver problems.
- have high blood pressure.
- had or now have a type of skin cancer called basal cell carcinoma (BCC), melanoma, or squamous cell carcinoma.
- have eye problems, especially an inflammation of the eye called uveitis.
- have diabetes.
- are pregnant or plan to become pregnant. PONVORY may harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant. If you are a woman who can become pregnant, you should use effective birth control during your treatment with PONVORY and for 1 week after you stop taking PONVORY. Talk to your healthcare provider about what method of birth control is right for you during this time. Tell your healthcare provider right away if you do become pregnant while taking PONVORY or within 1 week after you stop taking PONVORY.
- are breastfeeding or plan to breastfeed. It is not known if PONVORY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take PONVORY.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

Using PONVORY and other medicines together may affect each other causing serious side effects.

Especially tell your healthcare provider if you take or have taken:

- medicines to control your heart rhythm (antiarrhythmics), or blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers).
- medicines that affect your immune system, such as alemtuzumab.
- medicines such as rifampin, phenytoin, or carbamazepine.
- You should not receive **live** vaccines during treatment with PONVORY, for at least 1 month before taking PONVORY, and for 1 to 2 weeks after you stop taking PONVORY. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Vaccines may not work as well when given during treatment with PONVORY.

Talk with your healthcare provider if you are not sure if you take any of these medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take PONVORY?

You will receive a 14-day starter pack. You must start PONVORY by slowly increasing doses over the first two weeks. Follow the dose schedule in the table below. This may reduce the risk of slowing of the heart rate.

Starter Pack Day	Daily Dose
Day 1	2 mg tablet 1 time a day
Day 2	2 mg tablet 1 time a day
Day 3	3 mg tablet 1 time a day
Day 4	3 mg tablet 1 time a day
Day 5	4 mg tablet 1 time a day
Day 6	4 mg tablet 1 time a day
Day 7	5 mg tablet 1 time a day
Day 8	6 mg tablet 1 time a day
Day 9	7 mg tablet 1 time a day
Day 10	8 mg tablet 1 time a day
Day 11	9 mg tablet 1 time a day
Day 12	10 mg tablet 1 time a day
Day 13	10 mg tablet 1 time a day
Day 14	10 mg tablet 1 time a day

Maintenance	Daily Dose
Day 15 and thereafter	20 mg tablet 1 time a day

- Take PONVORY exactly as your healthcare provider tells you to take it.
- Take PONVORY 1 time each day.
- Swallow PONVORY tablets whole.
- Take PONVORY with or without food.
- Do not stop taking PONVORY without talking with your healthcare provider first.
- Do not skip a dose.
- Start taking PONVORY with a 14-day starter pack.
- If you miss taking 1, 2, or 3 tablets in a row of PONVORY in the 14-day starter pack, continue treatment by taking the first dose you missed. Take 1 tablet as soon as you remember. Then, take 1 tablet a day to continue with the starter pack dose as planned.
- If you miss taking 1, 2, or 3 tablets in a row of PONVORY while taking the 20 mg maintenance dose, continue treatment with the 20 mg maintenance dose.
- If you miss taking 4 or more tablets in a row of PONVORY, while taking the 14-day starter pack or the 20 mg maintenance dose, you need to restart treatment with a new 14-day starter pack. Call your healthcare provider if you miss 4 or more doses of PONVORY. Do not restart PONVORY after stopping it for 4 or more days in a row without talking to your healthcare provider. If you have certain heart conditions, you may need to be monitored by your healthcare provider for at least 4 hours when you take your next dose.
- Write down the date you start taking PONVORY so you will know if you miss 4 or more doses in a row.

What are the possible side effects of PONVORY?

PONVORY may cause serious side effects, including:

- See **"What is the most important information I should know about PONVORY?"**
- **breathing problems.** Some people who take PONVORY have shortness of breath. Call your healthcare provider right away if you have new or worsening breathing problems.
- **liver problems.** PONVORY may cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking PONVORY. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - unexplained nausea
  - vomiting
  - stomach (abdominal) pain
  - tiredness
  - loss of appetite
  - yellowing of the whites of your eyes or skin
  - dark urine
- **increased blood pressure.** Your healthcare provider should check your blood pressure during treatment with PONVORY.
- **types of skin cancer called basal cell carcinoma (BCC), melanoma, and squamous cell carcinoma.** Certain types of skin cancer have happened with drugs in the same class. Tell your healthcare provider if you have any changes in the appearance of your skin, including changes in a mole, a new darkened area on your skin, a sore that does not heal, or growths on your skin, such as a bump that may be shiny, pearly white, skin-colored, or pink. Your doctor should check your skin for any changes during treatment with PONVORY. Limit the amount of time you spend in sunlight and ultraviolet (UV) light. Wear protective clothing and use a sunscreen with a high sun protection factor.
- **a problem with your vision called macular edema**. Tell your healthcare provider about any changes in your vision. Your healthcare provider should test your vision before you start taking PONVORY and any time you notice vision changes during treatment with PONVORY. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

  Call your healthcare provider right away if you have any of the following symptoms:
  - blurriness or shadows in the center of your vision
  - a blind spot in the center of your vision
  - sensitivity to light
  - unusually colored (tinted) vision
- **swelling and narrowing of the blood vessels in your brain.** A condition called Posterior Reversible Encephalopathy Syndrome (PRES) has happened with drugs in the same class. Symptoms of PRES usually get better when you stop taking PONVORY. However, if left untreated, it may lead to a stroke. Call your healthcare provider right away if you have any of the following symptoms:
  - sudden severe headache
  - sudden confusion
  - sudden loss of vision or other changes in your vision
  - seizure
- **severe worsening of multiple sclerosis (MS) after stopping PONVORY.** When PONVORY is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your healthcare provider before you stop taking PONVORY for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping PONVORY.

The most common side effects of PONVORY include:

- upper respiratory tract infections
- elevated liver enzymes (abnormal liver tests)
- high blood pressure

These are not all of the possible side effects of PONVORY.

For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PONVORY?

- Store PONVORY at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Store PONVORY in the original package.
- The bottle of PONVORY contains a desiccant sachet to help keep your medicine dry (protect it from moisture). Do not throw away (discard) the desiccant.

Keep PONVORY and all medicines out of the reach of children.

General information about the safe and effective use of PONVORY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PONVORY for conditions for which it was not prescribed. Do not give PONVORY to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about PONVORY that is written for health professionals.

What are the ingredients in PONVORY?

Active ingredient: ponesimod

Inactive ingredients:
Tablet core: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, silica colloidal anhydrous, and sodium lauryl sulfate.

Tablet coating: ferrosoferric oxide (included in 4 mg, 5 mg, 8 mg and 9 mg film-coated tablets), hydroxypropyl methylcellulose 2910, iron oxide red (included in 3 mg, 4 mg, 7 mg, 8 mg, 9 mg and 10 mg film-coated tablets), iron oxide yellow (included in 3 mg, 5 mg, 7 mg, 9 mg, 10 mg and 20 mg film-coated tablets), lactose monohydrate, polyethylene glycol 3350, titanium dioxide, and triacetin.

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

For more information, go to www.ponvory.com or call 1-800-526-7736.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Approved: 03/2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALICE HUGHES
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