

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213498Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency**

Date: March 16, 2021

Reviewer: Silvia Perez-Vilar, PharmD, PhD  
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS  
Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MPH, MS  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: PONVORY (Ponesimod)

Application Type/Number: NDA 213498

Applicant/sponsor: Janssen Pharmaceuticals, Inc.

OSE RCM #: 2020-1787

## Expedited ARIA Sufficiency for Pregnancy Safety Concerns

### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

Ponesimod (PONVORY, Janssen Pharmaceuticals, Inc.) is a sphingosine-1-phosphate (S1P) receptor agonist, which binds selectively to one (S1P<sub>1</sub>) of the five known S1P receptors. It deprives lymphocytes of the obligatory signal to egress from lymphoid organs, preventing the recirculation of lymphocytes to other sites, and sequestering them in secondary lymphoid tissue.<sup>1,2</sup> The proposed indication is the treatment of relapsing forms of multiple sclerosis (MS) in adults. It is a new molecular entity (NME) and is not currently marketed in the United States for any indication. US-marketed S1P modulators for the treatment of relapsing forms of MS (RMS) include fingolimod (GILENYA), which was approved for the treatment of adults with RMS in 2010 and for individuals aged 10 years and up in 2018, siponimod (MAYZENT) and ozanimod (ZEPOSIA), which were approved for the treatment of adults with RMS in 2019 and 2020, respectively.<sup>3</sup>

S1P Products Indicated for the Treatment of Relapsing Forms of Multiple Sclerosis (Approval Year)	FDAAA Purpose (per Section 505(o)(3)(B))	PMR(s) for Pregnancy Safety
Fingolimod (GILENYA), 2010	Not applicable <sup>4</sup>	Yes; pregnancy exposure registry with external comparison group <sup>5</sup>
Siponimod (MAYZENT), 2019	Identify unexpected serious risk when available data indicate potential for serious risk	Yes; pregnancy exposure registry with internal and/or external comparison groups and electronic database study with outcome validation <sup>6</sup>
Ozanimod (ZEPOSIA), 2020	Identify unexpected serious risk when available data indicate potential for serious risk	Yes; pregnancy exposure registry with internal and/or external comparison groups and electronic database study with outcome validation <sup>7</sup>

<sup>1</sup> PONVORY (ponesimod). Draft clinical review dated January 27, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>2</sup> PONVORY (ponesimod). Draft non-clinical primary review dated January 26, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>3</sup> See footnote 1

<sup>4</sup> FDA activated the ARIA system in 2016

<sup>5</sup> Fingolimod (GILENYA). Approval letter dated September 21, 2010. Accessed on March 8, 2021 at [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2010/022527s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022527s000ltr.pdf)

<sup>6</sup> Siponimod (MAYZENT). Approval letter dated March 26, 2019. Accessed on March 8, 2021 at [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2019/209884Orig1s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2019/209884Orig1s000ltr.pdf)

<sup>7</sup> Ozanimod (ZEPOSIA). Approval letter dated March 25, 2020. Accessed on March 8, 2021 at [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2020/209899Orig1s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2020/209899Orig1s000ltr.pdf)



The mechanism by which ponesimod exerts therapeutic effects in MS may involve reduction of lymphocyte migration into the central nervous system.<sup>8</sup> The proposed maintenance dose is 20 mg once daily administered orally after a 14-day dose escalation; 2 mg on Days 1 and 2, 3 mg on Days 3 and 4, 4 mg on Days 5 and 6, 5 mg on Day 7, 6 mg on Day 8, 7 mg on Day 9, 8 mg on Day 10, 9 mg on Day 11, and 10 mg on Days 12, 13, and 14.<sup>9</sup> The time to reach maximum plasma concentration of ponesimod is 2–4 hours post-dose. Ponesimod is highly bound to plasma proteins, and is mainly distributed in the plasma fraction of whole blood; animal studies show that ponesimod readily crosses the blood-brain-barrier.<sup>10</sup> The elimination half-life after oral administration is approximately 33 hours.<sup>11</sup>

The New Drug Application (NDA) submission included data from a Phase 3, active-controlled (b) (4) randomized clinical trial (RCT), a Phase 2, placebo-controlled, dose-finding RCT, and their open label extensions. These data are supported by placebo-controlled studies in adults with plaque psoriasis and clinical pharmacology studies, most of which were in healthy adult volunteers. The safety signals identified with ponesimod appear similar to those of other S1P receptor modulators and include infections, lymphopenia, bradyarrhythmia and atrioventricular block, hepatic transaminase elevations suggestive of liver injury, hypertension, respiratory effects, and macular edema. Like other S1P receptor modulators, ponesimod may have an increased risk of (cutaneous) malignancies.<sup>12</sup> The proposed labeling (as of March 16, 2021) includes Warnings and Precautions for infections, bradyarrhythmia and atrioventricular conduction delays, respiratory effects, liver injury, increased blood pressure, cutaneous malignancies, macular edema, posterior reversible encephalopathy syndrome, unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune-modulating therapies, severe increase in disability and immune system effects after stopping PONVORY, and fetal risk.<sup>13</sup>

## 1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of ponesimod during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease and Prevention 2008, Food and Drug Administration 2014). MS is a chronic inflammatory disease of the central nervous system leading to demyelination and neurodegeneration. The vast majority of patients with MS initially follow a relapsing-remitting course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between (Katz Sand 2015). MS is commonly diagnosed in women of childbearing age and its incidence is two to three times higher in women than men. Women with MS are not less fertile and do not have more difficulty in completing a pregnancy to term

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<sup>8</sup> Proposed PONVORY labeling dated March 16, 2021

<sup>9</sup> PONVORY (ponesimod). Draft clinical review dated January 27, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>10</sup> PONVORY (ponesimod). Draft non-clinical primary review dated January 26, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>11</sup> PONVORY (ponesimod). Clinical Pharmacology Review dated February 1, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>12</sup> See footnote 9

<sup>13</sup> See footnote 8



compared with healthy controls (Voskuhl and Momtazee 2017). While evidence regarding the effect of MS on pregnancy is not entirely consistent, available data suggest that maternal MS may be associated with an increased rate of caesarean delivery and lower infant birth weights compared with women without MS (Kelly, Nelson et al. 2009).

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ponesimod. The ponesimod clinical trials required that sexually active subjects of reproductive potential (both men and women) use an effective form of contraception for the duration of the study. Women who became pregnant during the studies were required to discontinue the study drug, as were men whose female partners became pregnant during the studies. A total of 15 female subjects exposed to ponesimod became pregnant during the ponesimod MS trials. Of these, six led to delivery of a normal baby (gestational ages not stated), six resulted in elective terminations (one due to molar pregnancy, reasons for the others were not given), and three led to spontaneous abortions (gestational ages not stated).<sup>14</sup> Animal studies with oral ponesimod showed teratogenicity in rats and fetal lethality in both rats and rabbits. Malformations in rats included fused ascending aorta trunk, muscular ventricular septal defect, membranous ventricular septal defects, syndactyly, ectrodactyly, malrotated hindlimbs, and eye microphthalmia and rabbits had morphological changes in the cardiovascular and limb systems. The fetal NOAEL was 1 mg/kg/day in both rats and rabbits with the safety margin for fetal toxicity 0.2-fold in rat and rabbit based on plasma exposure. The F1 NOAEL (10 mg/kg/day) from the pre- and postnatal study was due to F1 pup deaths, decrease body weight gain, delay of developmental endpoints, increased motor fine movements and ambulatory movements, and reduced reproductive performance at the HD.<sup>15</sup>

The current proposed labeling, as of March 16, 2021, includes warnings and precautions for fetal risk. It states *“Based on animal studies, PONVORY may cause fetal harm [see Use in Specific Populations (8.1, 8.3)]. Because it takes approximately 1 week to eliminate PONVORY from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 1 week after stopping PONVORY treatment.”*

Section 8.1 (Pregnancy) states:

“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

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<sup>14</sup> PONVORY (ponesimod). Draft clinical review dated January 27, 2021. Division of Neurology 2. U.S. Food and Drug Administration

<sup>15</sup> PONVORY (ponesimod). Non-clinical primary review dated January 27, 2021. Division of Neurology 2. U.S. Food and Drug Administration



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."

Section 8.3 (Females and Males of Reproductive Potential) states:

"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)]."<sup>16</sup>

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

<sup>16</sup> Proposed PONVORY labeling dated March 16, 2021



- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

## 2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.<sup>†</sup>
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).<sup>†</sup>

<sup>†</sup> **If checked, please complete General ARIA Sufficiency Template.**

## 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☒ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☒ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study.

## 2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- ☐ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

**Outcomes:** ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.



Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

## 2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN2, as of February 11, 2021, for the PMRs related to pregnancy outcomes:

*"Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to PONVORY (ponesimod) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to PONVORY (ponesimod) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.*

*A pregnancy outcomes study using a different study design than provided for in PMR 4024-2 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to PONVORY (ponesimod) during pregnancy compared to an unexposed control population."*

## REFERENCES

Centers for Disease, C. and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products— Content and Format. Draft Guidance." Guidance for Industry Retrieved February 3, 2020, from <https://www.fda.gov/media/90160/download>.

Katz Sand, I. (2015). "Classification, diagnosis, and differential diagnosis of multiple sclerosis." Curr Opin Neurol **28**(3): 193-205.

Kelly, V. M., L. M. Nelson and E. F. Chakravarty (2009). "Obstetric outcomes in women with multiple sclerosis and epilepsy." Neurology **73**(22): 1831-1836.

Voskuhl, R. and C. Momtazee (2017). "Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding." Neurotherapeutics **14**(4): 974-984.



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**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** March 10, 2021

**To:** Kristen Haslam, Regulatory Project Manager  
Division of Neurology II (DN-II)

Tracy Peters, Associate Director for Labeling, DN-II

**From:** Christine Bradshaw, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for PONVORY™ (ponesimod) tablets, for oral use (Ponvory)

**NDA:** 213498

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In response to DN-II's consult request dated April 10, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Ponvory.

**Labeling:** OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN-II (Haslam) on February 23, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on March 10, 2020.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 30, 2020 (Maintenance Pack Carton and Container Labeling) and February 24, 2021 (Revised Starter Pack Carton and Container Labeling), and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or [Christine.Bradshaw@fda.hhs.gov](mailto:Christine.Bradshaw@fda.hhs.gov).

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: March 9, 2021

To: Kristen Haslam, BSN, RN  
Senior Regulatory Health Project Manager  
**Division of Neurology II (DN2)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Lonice Carter, MS, RN, CNL  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Christine Bradshaw, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): PONVORY (ponesimod)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213498

Applicant: Janssen Pharmaceuticals, Inc.

## 1 INTRODUCTION

On March 18, 2020, Janssen Pharmaceuticals, Inc., submitted for the Agency's review a New Drug Application (NDA)/ New Molecular Entity 213498 for PONVORY (ponesimod). The purpose of this NDA is to propose the indication for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on April 10, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for PONVORY (ponesimod) tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft PONVORY (ponesimod) MG received on March 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 23, 2021.
- Draft PONVORY (ponesimod) Prescribing Information (PI) received on March 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 23, 2021.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20



- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: March 8, 2021  
Requesting Office or Division: Division of Neurology 2 (DN 2)  
Application Type and Number: NDA 213498  
Product Name and Strength: Ponvory (ponesimod) tablet, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg  
Applicant/Sponsor Name: Janssen Pharmaceuticals, Inc.  
OSE RCM #: 2020-2310-1  
DMEPA Safety Evaluator: Beverly Weitzman, PharmD  
DMEPA Team Leader (Acting): Celeste Karpow, PharmD, MPH

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted an amendment with minor revisions to the outer and inner wallet (14-day starter pack) container labels received on February 24, 2021 for Ponvory. On February 11, 2021 (OSE # 2020-2310) we found the Applicant's proposed labels and labeling received on October 30, 2020 for Ponvory acceptable from a medication error perspective.<sup>a</sup> However, the Applicant submitted this amendment<sup>b</sup> of their own accord, for NDA 213498 on February 24, 2021. This amendment provides minor revisions to the outer and inner wallet (14-day starter pack) container labels for Ponvory as follows:

### Outer Wallet and Inner Wallet Starter Pack:

- Revised the statement (b) (4) to "This package is child resistant when closed."

### Inner Wallet Starter Pack:

- Revised the statement (b) (4) to "Fold over and close after each use."
- Added the statement "Do not separate or cut" and the corresponding image.

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<sup>a</sup> Weitzman B. Label and Labeling Review for Ponvory (NDA 213498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 11. RCM No.: 2020-2310.

<sup>b</sup> Amendment Cover Letter available via docuBridge: <\\CDSESUB1\evsprod\nda213498\0030\m1\us\cover.pdf>

The Division of Neurology 2 (DN2) requested we review the revised container labels (i.e., inner and outer wallet) for Ponvory (See Appendix A) to determine if they are acceptable from a medication error perspective.

## 2 CONCLUSION

We find the Applicant's revisions to the inner and outer wallet (14-day starter pack) container labels acceptable from a medication error perspective. We have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 24, 2021

- Container labels (Annotated version): Starter Pack Blister sleeve (outer wallet) and Blister Card (inner wallet)
- Container labels (Clean Version): Starter Pack Blister sleeve (outer wallet) and Blister Card (inner wallet)

Container labels

14-day Starter Pack Blister Card Sleeve (Outer Wallet):

Annotated Version:





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## MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

**Date:** March 4, 2021

**To:** Nicholas Kozauer, MD, Director (Acting)  
Division of Neurology II

**Through:** Dominic Chiapperino, PhD, Director  
Joshua Lloyd, MD, Medical Officer Team Leader  
Controlled Substance Staff

**From:** Shalini Bansil, MD, Medical Officer  
Controlled Substance Staff

**Subject:** **Product:** Ponesimod; Tradename Ponvory  
**Dosages:** 20 mg tablet taken orally once daily  
**NDA Number:** 213498, product developed under IND 101722  
**Indication(s):** Treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease  
**Applicant:** Janssen Pharmaceuticals  
**PDUFA Goal Date:** March 18, 2021

### Materials Reviewed:

- Abuse-related data in Original NDA submission dated March 18, 2020, and subsequent amendments
- Randall-Thompson, J; DARRTS IND 101722; September 20, 2019

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## I. SUMMARY

### 1. Background

This memorandum responds to a consult request from the Division of Neurology II (DN2), dated April 10, 2020, to the Controlled Substance Staff (CSS) to evaluate the abuse-related nonclinical and clinical data submitted for ponesimod (tradename **Ponvory**) by Janssen Pharmaceuticals (referred to as “the Applicant”) under NDA **213498** and developed under IND **101722**. Ponesimod is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

Ponesimod (codename JNJ-67896153/ACT-128800) is an (b) (4) derivative and is an orally-active, selective modulator of the sphingosine 1-phosphate receptor 1 (S1P1). The Applicant states that ponesimod binds with high affinity to S1P1 receptors located on lymphocytes and in other cell types, e.g., cardiomyocytes. 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 its therapeutic effects in multiple sclerosis may involve reduction of lymphocyte migration into the central nervous system. The effect of ponesimod on circulating effector T and B-cells represents a therapeutic approach for immune disorders, such as multiple sclerosis (MS), in which activated T- and B-cells play a critical role. The proposed dosage recommendation for ponesimod in adults is 20 mg once daily, following a gradual 14-day up-titration regimen.

Fingolimod (Gilenya, NDA 022527, approved in 2010, a non-selective S1P receptor modulator), siponimod (Mayzent, NDA 209884, approved in 2019, a selective S1P1 and S1P5 receptors modulator), and ozanimod (Zeposia, NDA 209899, approved in 2020, binds with high affinity to S1P receptors 1 and 5) are approved medications in this class (i.e., S1P receptor agonists) for the treatment of multiple sclerosis. These drugs are not scheduled under the Controlled Substances Act (CSA).

Based on the non-clinical and clinical data, the Applicant concludes that ponesimod does not meet the criteria to be scheduled under the CSA.

## 2. Conclusions

- The existing clinical and nonclinical data are not consistent with ponesimod having abuse potential, as evidenced by:
  - Ponesimod does not bind to abuse-related targets and does not induce acute CNS- and discontinuation/withdrawal-related symptoms or behaviors in animals (Randall-Thompson, J; DARRTS IND 101722; September 20, 2019)
  - Abuse-related adverse events were not identified in Phase 2/3 clinical studies
- Fingolimod, siponimod, and ozanimod, i.e., other approved S1P receptor agonists, showed no signals of abuse potential to warrant scheduling under the CSA, suggesting that ponesimod is not likely to have abuse potential
- In some Phase 1 clinical studies of ponesimod, there were unexplained occurrences of “euphoric mood” reported by healthy volunteers, which may be indicative of abuse potential. However, the totality of data are not convincing to conclude that ponesimod has meaningful abuse potential.
- Based on the available data, we agree with the Applicant that scheduling under the CSA is not warranted for ponesimod
- However, we recommend that the Applicant actively monitor for abuse and abuse potential of ponesimod in the post-marketing setting

## 3. Recommendations:

- We do not recommend that ponesimod be scheduled under the Controlled Substances Act (CSA)
- Section 9 Drug Abuse and Dependence of the labeling is not warranted for this product
- However, we recommend that the Applicant monitor for abuse and abuse potential of ponesimod in the post-marketing setting given the signal of unexplained cases of “euphoric mood” in some Phase 1 clinical studies of ponesimod, which may be indicative of abuse potential. The following request should be sent to the Applicant as part of the action letter:

### REQUESTED PHARMACOVIGILANCE

We request that you perform post marketing surveillance for cases of abuse or abuse-related adverse events in patients exposed to ponesimod. Submit individual reports as 15-day expedited reports to your NDA and directly to the Division of Neurology II. Include comprehensive summaries and analyses of these events quarterly as part of your required post marketing safety reports (e.g., periodic safety update reports [PSURs]). In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the occurrence of abuse or abuse-related adverse events in patients exposed to ponesimod or the causality, along with information about dose and dose titration, duration of ponesimod therapy, time of event in relation to

duration of therapy, associated signs and symptoms, concomitant therapies, treatment given for the event, and outcome of each event.

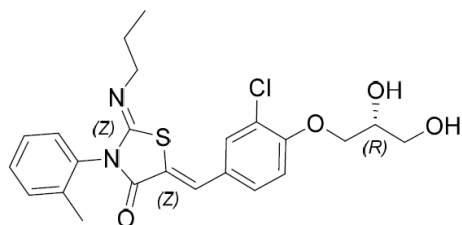
## II. DISCUSSION

### 1. Chemistry

Information about the drug substance and product was obtained from the Applicant's NDA submission.

#### 1.1 Substance Information

Molecular formula: C<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub>S



Ponesimod is a white to light yellowish powder. Ponesimod is poorly soluble in aqueous media over the pH range of 1-7.5.

#### 1.2 Drug Product

Ponesimod is supplied as immediate-release film-coated tablets for oral use at the dosage strengths of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg. The excipients used in the drug product are standard pharmaceutical excipients. (b) (4) is used for the coating of the film-coated tablets. The coating powder (b) (4) is not described in any pharmacopoeial monograph. However, the individual components of the coating powder are compendial.

### 2. Nonclinical Pharmacology

The abuse potential of ponesimod was not assessed in dedicated nonclinical studies. Ponesimod does not bind to abuse-related targets and does not induce acute CNS- and discontinuation/withdrawal-related symptoms or behaviors in animals (Randall-Thompson, J; DARRTS IND 101722; September 20, 2019).

### 3. Clinical Pharmacology

Refer to the Clinical Pharmacology review in DARRTS for a complete discussion of the clinical pharmacology data submitted in this application.

### 4. Clinical Studies

#### 4.1 Human Abuse Potential Studies

No human abuse potential studies were conducted on ponesimod, which is acceptable since the approved medications in this class (i.e., S1P receptor agonists) are not scheduled under the CSA. Additionally, clinical trials conducted on ponesimod did not indicate clear evidence of abuse potential.



#### 4.2 Adverse Event Profile Through all Phases of Development

The Applicant conducted Phase 1 and Phase 2/3 studies as part of the clinical development program for ponesimod. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs reported during different phases of clinical development.

##### Phase 1 Studies:

**Table 1** displays the abuse-related AEs reported in single-dose, Phase 1 studies.

**Table 1:** Abuse-related adverse events: Single-dose, Phase 1 studies

Study	Ponesimod dose	Number of subjects	Abuse-related adverse events n (%)
AC-058-103	20 mg	12 healthy subjects	none
AC-058-108	40 mg	14 healthy subjects	Euphoric mood 1 (7%); somnolence 1 (7%)
AC-058-114	5mg IV; 10 mg oral	14 healthy subjects	none
AC-058-106	40 mg	6 healthy subjects	none
AC-058-107	40 mg	20 healthy subjects	Euphoric mood 3 (15%); somnolence 3 (15%); depressed mood 1 (5%); Feeling of relaxation 1(5%); irritability 1 (5%); lethargy 1 (5%); memory impairment 1 (5%)
AC-058-112	10 mg	32 subjects: healthy and with hepatic impairment	none
AC-058-113	10 mg	24 subjects with renal impairment	none

AC-058-101: This was a Phase 1 single ascending dose study in healthy subjects. Ponesimod at doses of 1 mg to 75 mg were administered to 36 subjects, and 12 subjects received placebo. Euphoric mood was reported in one subject who received 75 mg of ponesimod.

**Table 2** displays the abuse-related adverse events reported in multiple-dose Phase 1 studies in healthy subjects.

**Table 2:** Abuse-related adverse events: Multiple-dose Phase 1 studies in healthy subjects

Study	Ponesimod dose	Number of subjects	Abuse-related adverse events n (%)
AC-058-102	5 mg-40 mg	47	none
AC-058-105	2.5 mg-20 mg	29	Hyperhidrosis 1(3.4%); somnolence 1(3.4%)
AC-058-109	10 mg-100 mg	12 ponesimod; 4 placebo	Ponesimod: Lethargy1(8.3%); sensory disturbance1(8.3%); somnolence 1(8.3%) Placebo: none
AC-058-115	2mg-20mg	24 ponesimod; 16 placebo	Ponesimod: Somnolence 2 (8.3%); irritability 1 (4.2%); feeling abnormal 1 (4.2%) Placebo: Somnolence 3 (18.8%) lethargy 1 (6.3%); energy increased 1 (6.3%)

AC-058-110: This was a Phase 1 multiple-dose study to determine the effects of ponesimod on the QTc interval. Healthy subjects were enrolled. Group A received ponesimod (10 mg-100 mg) and Group B received moxifloxacin or placebo. The abuse-related AEs are displayed in **Table 3**.

**Table 3:** Abuse-related adverse events: Study AC-058-110 n (%)

	Ponesimod N=58	Moxifloxacin or placebo N=57
Somnolence	9 (15.5%)	7 (12.3%)
Mood altered	1 (1.7%)	3 (5.3%)
Irritability	1 (1.7%)	0
Anxiety	1 (1.7%)	5 (8.8%)
Hyperhidrosis	3 (5.2%)	0
Euphoric mood	5 (8.6%)	2 (3.5%)
Cognitive disorder	0	1 (1.8%)

#### Drug-Drug interaction Phase 1 studies:

AC-058-104: This study evaluated the potential for interaction between Ortho-Novum (norethisterone and ethinyl estradiol) and ponesimod (10 mg-40 mg) in 22 healthy females. No abuse related AEs were reported.

AC-058-111: This study evaluated the potential for interaction between atenolol, diltiazem and ponesimod (10 mg). The study was prematurely discontinued due to safety reasons of cardiac toxicity. Somnolence was the only abuse-related AE reported, and it occurred in four of eight subjects taking ponesimod.

AC-058-117: This study evaluated the potential for interaction between propranolol and ponesimod (2 mg-20 mg). Restlessness and somnolence were reported with the combination and with ponesimod alone.

Reports of euphoric mood in Phase 1 studies:

There were reports of euphoric mood in 4 of the 16 Phase 1 studies (i.e., AC-058-108 [ponesimod 40 mg]; AC-058-101 [ponesimod 75 mg]; AC-058-107 [ponesimod 40 mg]; and AC-058-110 [ponesimod 10 mg-100 mg]).

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] However, we do not concur with this explanation as [REDACTED] (b) (4)  
[REDACTED].

Euphoric mood was also reported in Study AC-058-110, in which a cluster of these events was reported (euphoric mood was reported in five of 58 subjects on ponesimod and two of 57 subjects on moxifloxacin/placebo). The Applicant states that they performed a detailed review of source documents for these AEs and, in most cases, there appeared to be a discrepancy between the symptoms described by the subject/nurse and the physician reported term. Source documents revealed that most of these events were initially recorded as disorientation and subsequently coded as euphoric mood by the physician. [REDACTED] (b) (4)  
[REDACTED]

Upon review of the source documents for subjects in whom euphoric mood was reported in Study AC-058-110, CSS noted that three of five subjects in the ponesimod group and both subjects in the moxifloxacin/placebo group were appropriately coded as euphoric mood. Two subjects in the ponesimod group reported feeling disoriented, 'in a fog,' 'cloudy mind,' and these were coded as euphoric mood.

Phase 1 Studies Conclusions: The occurrence of euphoric mood in four Phase 1 studies may indicate that ponesimod has abuse potential. We disagree with the Applicant that [REDACTED] (b) (4)  
[REDACTED]. The occurrence of euphoric mood at supratherapeutic doses (40 mg, 75 mg) of ponesimod in some studies is further suggestive of abuse potential.

However, in two of these studies, there was no placebo group (AC-058-108 and AC-058-107), thus, it is unclear if euphoric mood was related to ponesimod. In Study AC-058-101, only one subject on ponesimod reported euphoric mood and no subject on placebo reported this AE. In Study AC-058-110, euphoric mood was reported in five of 58 subjects on ponesimod and two of 57 subjects on moxifloxacin/placebo. It is possible that two subjects in the ponesimod group were inaccurately coded as having an AE of euphoric mood.

In summary, the adverse events in Phase 1 studies of ponesimod do not definitively indicate the presence or absence of abuse potential.

Phase 2/3 studies:

A multicenter, randomized, double-blind, placebo controlled, parallel-group, dose-finding study to evaluate the efficacy, safety, and tolerability of three doses of ponesimod (ACT-128800), an oral S1P1 receptor agonist, administered for twenty-four weeks in patients with relapsing-remitting multiple sclerosis AC-058-B201. Phase2b.

The primary objective was to demonstrate the efficacy of at least one of three doses of ponesimod as compared to placebo in patients with relapsing-remitting multiple sclerosis (RRMS) on the cumulative number of new gadolinium-enhancing lesions per patient, recorded on T1-weighted magnetic resonance imaging (MRI) scans at Weeks 12, 16, 20, and 24 after study drug initiation.

This was a Phase 2b, prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, four arm, parallel-group, dose-finding study. Patients were randomized in a 1:1:1:1 ratio (10 mg ponesimod: 20 mg ponesimod: 40 mg ponesimod: placebo). Study drug was administered for a period of 24 weeks. Adult male and female patients aged 18 to 55 years with a diagnosis of relapsing-remitting multiple sclerosis (RRMS) were included. 464 patients were randomized in the study; 108, 116, 119, and 121 patients randomized to the ponesimod 10 mg, 20 mg, and 40 mg, and placebo groups, respectively. All but two randomized patients (ponesimod 20 mg) received treatment with study drug.

**Table 4** displays the abuse-related adverse events.

**Table 4:** Abuse-related adverse events: Study AC-058-B201

	Ponesimod 40 mg N=119 n (%)	Ponesimod 20 mg N=114 n (%)	Ponesimod 10 mg N=108 n (%)	Placebo N=121 n (%)
Anxiety	4 (3.4)	3 (2.6)	5 (4.6)	0
Depression	4 (3.4)	3 (2.6)	1 (0.9)	1 (0.8)
Disturbance in attention	2 (1.7)	0	0	0
Somnolence	1 (0.8)	0	3 (2.8)	0
Irritability	1 (0.8)	1 (0.9)	0	1 (0.8)
Hyperhidrosis	1 (0.8)	0	0	1 (0.8)
Memory impairment	1 (0.8)	0	0	0
Affect lability	0	0	0	3 (2.5)
Agitation	0	0	1 (0.9)	2 (1.7)
Mood altered	0	2 (1.8)	1 (0.9)	0
Confusional state	0	0	1 (0.9)	0
Dysphoria	0	0	1 (0.9)	0
Hypersomnia	0	1 (0.9)	0	0
Nervousness	0	0	1 (0.9)	0
Psychomotor hyperactivity	0	0	0	1 (0.8)
Restlessness	0	1 (0.9)	0	0

Multicenter, Randomized, Double-Blind, Parallel group, Active-Controlled, Superiority Study to Compare the Efficacy and Safety of Ponesimod to Teriflunomide in Subjects With Relapsing Multiple Sclerosis AC-058-B301. Phase 3.

This study was performed to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses in subjects with relapsing multiple sclerosis (RMS). This was a prospective, multicenter, randomized, double-blind, active-controlled, parallel group, Phase 3, superiority study, designed to compare the efficacy, safety, and tolerability of ponesimod 20 mg versus teriflunomide 14 mg in adult subjects with RMS.

A total of 1133 subjects were randomized in a 1:1 ratio to receive ponesimod 20 mg or teriflunomide 14 mg. The study comprised the following periods: Prerandomization, 108-week treatment period, and a posttreatment follow-up period. **Table 5** displays the abuse-related adverse events.

**Table 5:** Abuse related adverse events: Study AC-058-B301

	Ponesimod 20 mg N=565 n (%)	Teriflunomide 14 mg N=566 n (%)
Somnolence	18 (3.2)	9 (1.6)
Cognitive disorder	4 (0.7)	0
Disturbance in attention	3 (0.5)	3 (0.5)
Memory impairment	2 (0.4)	1 (0.2)
Sensory disturbance	2 (0.4)	4 (0.7)
Amnesia	0	1 (0.2)
Lethargy	0	2 (0.4)
Drug withdrawal syndrome	1 (0.2)	0
Energy increased	1 (0.2)	0
Feeling abnormal	1 (0.2)	2 (0.4)
Hyperhidrosis	2 (0.4)	1 (0.2)
Depression	21 (3.7)	29 (5.1)
Anxiety	18 (3.2)	16 (2.8)
Depressed mood	3 (0.5)	5 (0.9)
Depressive disorder	2 (0.4)	0
Hallucination auditory	1 (0.2)	0
Suicidal ideation	1 (0.2)	0
Affect lability	0	4 (0.7)
Agitation	0	1 (0.2)
Confusional state	0	1 (0.2)
Derealization	0	1 (0.2)
Disorientation	0	1 (0.2)
Irritability	0	1 (0.2)
Restlessness	0	1 (0.2)



(b) (4)

Multicenter, Non-Comparative Extension to Study AC-058B301, to Investigate the Long-Term Safety, Tolerability, and Control of Disease of Ponesimod 20 mg in Subjects With Relapsing Multiple Sclerosis AC-058-B303. Phase 3.

The aim of this study was to describe the long-term (LT) safety and tolerability of ponesimod 20 mg in subjects with relapsing multiple sclerosis (RMS). This is an ongoing prospective, multicenter, open-label, non-comparative, LT extension of the Phase 3 confirmatory core study AC-058-B301. Subjects who completed the 108-week double-blind (DB) treatment period in the core study were enrolled into one group treated with ponesimod 20 mg once daily. After completing the core study follow-up period, eligible subjects were transitioned into the extension study. The extension study comprises 3 periods: pretreatment period, treatment period (up to 240 weeks), and a safety follow up. Of the subjects randomized in the core study, 877 subjects (439 on ponesimod 20 mg and 438 on teriflunomide 14 mg) were enrolled in the extension study. All subjects received ponesimod 20 mg in the extension study. The abuse related adverse events are displayed in **Table 6**.

**Table 6:** Abuse-related adverse events: Study AC-058-B303.

	Ponesimod/Ponesimod N=439; n (%)	Teriflunomide/Ponesimod N=438; n (%)
Disturbance in attention	1 (0.2)	0
Memory impairment	1 (0.2)	1 (0.2)
Somnolence	1 (0.2)	3 (0.7)
Anxiety	3 (0.7)	6 (1.4)
Depression	2 (0.5)	6 (1.4)
Affect lability	1 (0.2)	0
Agitation	1 (0.2)	0
Apathy	1 (0.2)	0
Irritability	1 (0.2)	0
Mood Swings	1 (0.2)	0
Anxiety disorder	0	4 (0.9)
Depressed mood	0	2 (0.5)
Neurosis	0	1 (0.2)
Psychotic disorder	0	1 (0.2)

Multicenter, Randomized, Double-blind, Parallel-group Extension to Study AC-058B201 to Investigate the Long-term Safety, Tolerability, and Efficacy of 10, 20, and 40 mg/day Ponesimod, an Oral S1P1 Receptor Agonist, in Patients With Relapsing-remitting Multiple Sclerosis. AC-058-B202. Phase 2.

The aim of this study was to investigate the long-term safety and tolerability of ponesimod. An interim report describes the results of an interim analysis of the B202 extension study, based on data up to a clinical cutoff date of 31 March 2019. This analysis includes combined data from the completed Phase 2b Study B201 (also referred to as the ‘core study’) and its extension study, Study B202 (also referred to as the ‘extension study’). Study B202 is an ongoing, prospective, multicenter, multinational, randomized, double-blind, multiple-dose, uncontrolled, parallel-group extension study in patients with RRMS who completed the core study. A total of 393 subjects completed treatment in the core study, of whom 353 entered the extension study (B202). Subjects were treated for 24 weeks during the core study and for up to 528 weeks during the extension study. **Depression** occurred in 6.2% of subjects, **anxiety** in 5.1% of subjects, and **somnolence** in 1.4% of subjects. Other possible AEs that may signal abuse potential, including memory impairment, disturbance in attention, hypersomnia, mood altered, restlessness, agitation, cognitive disorder, hyperhidrosis, confusional state, psychotic disorder, and irritability, occurred in less than 1% of subjects. In the 120 day update, no further abuse potential related AEs were reported.

(b) (4)

Multicenter, randomized, double-blind, placebo controlled, Phase IIa study to evaluate the efficacy, safety, and tolerability of ACT-128800, an S1P1 receptor agonist, administered for 6 weeks to subjects with moderate to severe chronic plaque psoriasis. AC-058-A200. Phase 2a.

This was a prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 2a study. Following a 14- to 28-day screening period, eligible subjects received either ACT-128800 or matching placebo for 6 weeks. Sixty-six (66) subjects with moderate to severe plaque psoriasis were recruited and analyzed (45 in the ACT-128800 group, 21 in the placebo group). The mean daily dose was 18.6 mg in the ACT-128800 group. Disturbance in attention was noted in 1/45 subjects in the ACT-128800 group.

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of two doses of ponesimod (ACT-128800), an oral S1P1 receptor agonist, administered up to twenty-eight weeks in patients with moderate to severe chronic plaque psoriasis. AC-058-A201. Phase 2.

This was a prospective, multicenter, multinational, double-blind, randomized, placebo-controlled, three-arm, parallel group, dose-finding study that evaluated the efficacy, safety and tolerability of two oral once-daily doses of ponesimod (20 mg [n=126] and 40 mg [n=133]) versus placebo (n=67) for a duration of 28 weeks. No abuse-related AEs were reported.

Phase 2/3 Study Conclusions: The Phase 2/3 studies did not report the occurrence of any adverse events of euphoric mood. Anxiety, depression, and somnolence were reported and may be associated with

abuse potential, but these AEs in the absence of other AEs such as euphoria, hallucinations, feeling jittery, depersonalization, derealization, which are more strongly indicative of abuse potential, are unlikely to suggest that ponesimod has abuse potential. When ponesimod was compared to teriflunomide, an unscheduled immunomodulator used in MS treatment, rates of anxiety, depression, and somnolence were similar in the two drugs. Depression and anxiety are commonly associated with chronic illnesses such as MS.

#### 4.3 Safety Profile

The major non-abuse-related adverse events of ponesimod in clinical trials include infections / lymphopenia, first dose bradyarrhythmia and AV block, respiratory effects (decrease in vital capacity), transaminase elevations, increased blood pressure, macular edema, cutaneous malignancies, and fetal risks.

#### 4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Drug accountability was performed at every scheduled visit in all Phase 2 and 3 clinical studies. Subjects were required to bring back all unused study medication as well as empty medication kits. If study drug had been lost or damaged or kits were not returned, or if the number of tablets returned did not match the expected number, this was to be reported as a protocol deviation. According to the Applicant, overall, events of drug accountability irregularities and study dropouts for reasons of possible noncompliance were observed in all treatment groups from all clinical studies and do not appear to indicate a clear pattern of drug seeking behavior in study subjects. Overdose related to ponesimod during the Phase 2 and Phase 3 clinical trials was related to medication errors (i.e., taking 2 tablets instead of 1 tablet on one occasion), was observed in both ponesimod and control (teriflunomide) groups, and was not considered to be related to abuse, diversion or drug-seeking behavior.

#### 4.5 Tolerance and Physical Dependence Studies in Humans

Dependence and withdrawal have not been specifically studied in subjects treated with ponesimod. Discontinuation-emergent AEs were recorded.

Study AC-058-B201: Analysis of discontinuation-emergent AEs experienced by subjects in AC-058-B201 demonstrated that there was no difference in the overall frequency of AEs reported in subjects treated with ponesimod as compared to placebo.

Study AC-058-B301: To compare the effects of ponesimod versus teriflunomide, discontinuation emergent AEs reported by subjects in AC-058B301 were determined. The overall frequency of discontinuation-emergent AEs was comparable between the two treatment groups.

Thus, withdrawal symptoms, which may indicate physical dependence, did not occur upon discontinuation of ponesimod.

### 5. Regulatory Issues and Assessment

Ponesimod does not display clear evidence of abuse potential. Ponesimod does not bind to abuse-related targets and does not induce acute CNS- and discontinuation/withdrawal-related symptoms or behaviors in animals. Ponesimod does not produce abuse-related adverse events in Phase 2/3 clinical studies. Additionally, fingolimod, siponimod, and ozanimod, i.e., other approved S1P receptor agonists, are not scheduled under the CSA. However, in some Phase 1 clinical studies of ponesimod, unexplained

occurrences of “euphoric mood” occurred, which may be indicative of abuse potential. Therefore, although we do not recommend scheduling of ponesimod under the CSA, we do recommend that the Applicant proactively monitor for abuse and abuse potential of ponesimod in the post-marketing setting.

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**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.**  
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/s/  
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SHALINI M BANSIL  
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JOSHUA M LLOYD  
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DOMINIC CHIAPPERINO  
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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum:	February 11, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 213498
Product Name and Strength:	Ponvory (ponesimod) tablet, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2020-2310
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader (Acting):	Celeste Karpow, PharmD, MPH

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling on October 30, 2020 for Ponvory. The Division of Neurology 2 (DN2) requested that we review the revised container labels and carton labeling for Ponvory (See Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

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<sup>a</sup> Weitzman B. Label and Labeling Review for Ponvory (NDA 213498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 17. RCM No.: 2020-533.

## 2 ASSESSMENT (ADDITIONAL INFORMATION FOR 14-DAY STARTER PACK PACKAGING CONFIGURATION DESIGN)

We identified that the presentation of sequencing of the proposed 14-day starter pack packaging configuration may contribute to two types of potential titration schedule errors, which may result in wrong dose medication errors if it is not understood by users. Specifically,

(b) (4)

both of which

would result in wrong dose errors during the titration phase.

Thus, the sponsor submitted additional information on October 30, 2020 to address our concerns of the proposed starter pack design. We reviewed the additional information and we did not identify any such signals or significant clinical concerns from a medication error perspective.

Furthermore, we consulted with the Medical Officer to assess the potential clinical impact and negative clinical consequences of potential wrong dose medication errors. The Medical Officer noted in reviewing the safety database that "there were 4 patients with a reported 20 mg overdose and none of them reported significant symptoms." The Medical officer further noted that the sponsor provided 'several studies' worth of data including studies using different titration regimens, and that one of these regimens included a titration that had a transition

(b) (4)

Accordingly, the Medical Officer confirmed that wrong dose errors during titration does not appear to be a significant concern. In addition, the MO noted that they do not have a concern that a dosing error during titration would yield a clinically significant adverse event or have a significant impact to the patient.

Considering the totality of the aforementioned information, including the lack of meaningful clinical impact associated with the potential errors, we find that the residual risk associated with potential wrong dose medication errors with the proposed starter pack design of this product has been minimized to an acceptable level, and we have no recommendations at this time.

## 3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

## APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 30, 2020

- Container labels: Starter Pack Blister sleeve (outer wallet), Blister Card (inner wallet) and Maintenance Dose (Bottle) (including Applicants response to our labeling recommendations)
- Carton labeling: 14-day Starter Pack and Maintenance dose (including Applicants response to our labeling recommendations).

Excerpt from submission:

Available in docuBridge via: <\\CDSESUB1\evsprod\nda213498\0023\m1\us\response-fda-ir-24sep2020.pdf>

### FDA Comments on Container Labels and Carton Labeling

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (Container Labels and Carton Labeling)			
1.	The labels and labeling contain the placeholder, "Tradename".	We reference our August 21, 2020 Proprietary Name Conditionally Acceptable Letter informing you that the proprietary name, Ponvory, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Ponvory, and use the intend-to-market font, color, etc.
2.	The format for expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective (e.g., risk for deteriorated drug medication errors).	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

#### 1.1. Applicant's Response

The Applicant has replaced "Tradename" with "Ponvory™" where it appears on Container Labels and Carton Labeling. For the expiration date format, the Applicant will be using an all-numeric expiration date format "YYYY-MM". This format is included as an annotation outside of the dieline in close proximity to the area in which the expiration date will be printed.

Additionally, minor technical template changes have been made as a result of changes made by the packaging site. Specifically, the color of the variable data prefixes and the GTIN number on the Starter Pack Carton was changed from (b) (4) (since this information will now be (b) (4) and the order of the position of the information for EXP and LOT was updated as follows:

GTIN

SN

LOT

EXP



## FDA Comments on Starter Pack Carton Labeling

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Starter Pack Carton Labeling			
1.	It is not clear that the starter pack is a [REDACTED] titration pack.	Can be improved for clarity.	Consider clarifying that the starter pack is a “14-day titration starter pack”.

### Applicant's Response

The Applicant agrees with the Agency's comment that adding [REDACTED] (b) (4) on the Starter Pack Labeling could help improve clarity for patients. Accordingly, the Applicant has revised the text to read “14-day Starter Pack” and has re-positioned this text for clarity. Consistent with other MS therapies that involve up-titration regimens (e.g., siponimod, ozanimod), the term “titration” was not added.

### Container labels

14-day Starter Pack Blister Card Sleeve (Outer Wallet):

(b) (4)

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/s/  
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BEVERLY WEITZMAN  
03/01/2021 03:47:44 PM

CELESTE A KARPOW  
03/01/2021 04:06:10 PM

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: February 11, 2021  
Requesting Office or Division: Division of Neurology 2 (DN 2)  
Application Type and Number: NDA 213498  
Product Name and Strength: Ponvory (ponesimod) tablet, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg  
Applicant/Sponsor Name: (b) (4)  
OSE RCM #: 2020-2310  
DMEPA Safety Evaluator: Beverly Weitzman, PharmD  
DMEPA Team Leader (Acting): Celeste Karpow, PharmD, MPH

---

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling on October 30, 2020 for Ponvory. The Division of Neurology 2 (DN2) requested that we review the revised container labels and carton labeling for Ponvory (See Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

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<sup>a</sup> Weitzman B. Label and Labeling Review for Ponvory (NDA 213498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 17. RCM No.: 2020-533.

## 2 ASSESSMENT (ADDITIONAL INFORMATION FOR 14-DAY STARTER PACK PACKAGING CONFIGURATION DESIGN)

We identified that the presentation of sequencing of the proposed 14-day starter pack packaging configuration may contribute to two types of potential titration schedule errors, which may result in wrong dose medication errors if it is not understood by users. Specifically,

(b) (4)

both of which

would result in wrong dose errors during the titration phase.

Thus, the sponsor submitted additional information on October 30, 2020 to address our concerns of the proposed starter pack design. We reviewed the additional information and we did not identify any such signals or significant clinical concerns from a medication error perspective.

Furthermore, we consulted with the Medical Officer to assess the potential clinical impact and negative clinical consequences of potential wrong dose medication errors. The Medical Officer noted in reviewing the safety database that "there were 4 patients with a reported 20 mg overdose and none of them reported significant symptoms." The Medical officer further noted that the sponsor provided 'several studies' worth of data including studies using different titration regimens, and that one of these regimens included a titration that had a transition

(b) (4)

Accordingly, the Medical Officer confirmed that wrong dose errors during titration does not appear to be a significant concern. In addition, the MO noted that they do not have a concern that a dosing error during titration would yield a clinically significant adverse event or have a significant impact to the patient.

Considering the totality of the aforementioned information, including the lack of meaningful clinical impact associated with the potential errors, we find that the residual risk associated with potential wrong dose medication errors with the proposed starter pack design of this product has been minimized to an acceptable level, and we have no recommendations at this time.

## 3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

## APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 30, 2020

- Container labels: Starter Pack Blister sleeve (outer wallet), Blister Card (inner wallet) and Maintenance Dose (Bottle) (including Applicants response to our labeling recommendations)
- Carton labeling: 14-day Starter Pack and Maintenance dose (including Applicants response to our labeling recommendations).

Excerpt from submission:

Available in docuBridge via: <\\CDSESUB1\evsprod\nda213498\0023\m1\us\response-fda-ir-24sep2020.pdf>

### FDA Comments on Container Labels and Carton Labeling

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (Container Labels and Carton Labeling)			
1.	The labels and labeling contain the placeholder, "Tradename".	We reference our August 21, 2020 Proprietary Name Conditionally Acceptable Letter informing you that the proprietary name, Ponvory, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Ponvory, and use the intend-to-market font, color, etc.
2.	The format for expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective (e.g., risk for deteriorated drug medication errors).	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

#### 1.1. Applicant's Response

The Applicant has replaced "Tradename" with "Ponvory™" where it appears on Container Labels and Carton Labeling. For the expiration date format, the Applicant will be using an all-numeric expiration date format "YYYY-MM". This format is included as an annotation outside of the dieline in close proximity to the area in which the expiration date will be printed.

Additionally, minor technical template changes have been made as a result of changes made by the packaging site. Specifically, the color of the variable data prefixes and the GTIN number on the Starter Pack Carton was changed from (b) (4) (since this information will now be (b) (4) and the order of the position of the information for EXP and LOT was updated as follows:

GTIN

SN

LOT

EXP

## FDA Comments on Starter Pack Carton Labeling

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Starter Pack Carton Labeling			
1.	It is not clear that the starter pack is a (b) (4) titration pack.	Can be improved for clarity.	Consider clarifying that the starter pack is a “14-day titration starter pack”.

## Applicant’s Response

The Applicant agrees with the Agency’s comment that adding (b) (4) on the Starter Pack Labeling could help improve clarity for patients. Accordingly, the Applicant has revised the text to read “14-day Starter Pack” and has re-positioned this text for clarity. Consistent with other MS therapies that involve up-titration regimens (e.g., siponimod, ozanimod), the term “titration” was not added.

## Container labels

14-day Starter Pack Blister Card Sleeve (Outer Wallet):

(b) (4)

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/s/  
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BEVERLY WEITZMAN  
02/11/2021 11:40:49 AM

CELESTE A KARPOW  
02/12/2021 10:01:35 AM

## Memo To File

<b>Date</b>	11/30/2020
<b>From</b>	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Kristen Haslam, Regulatory Project Manager David Jones, M.D., Medical Officer Paul Lee, M.D., Team Leader Division of Neurology 2 Office of Neuroscience
<b>NDA #</b>	213498
<b>Applicant</b>	Janssen Pharmaceuticals, Inc.
<b>Drug</b>	Ponesimod
<b>NME</b>	Yes
<b>Proposed Indication</b>	Treatment of relapsing forms of multiple sclerosis in adults
<b>Consultation Request Date</b>	4/29/2020
<b>Summary Goal Date</b>	12/18/2020
<b>Priority/Standard Review</b>	Standard
<b>Action Goal Date</b>	3/18/2021
<b>PDUFA Date</b>	3/18/2021

OSI received a consult from the Division of Neurology 2 (DN2) on 4/29/2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections:

- Dr. Evica Dincic (Site 2601, Serbia)
- Dr. Ivan Staikov (Site 2707, Bulgaria)

An inspection assignment for these four sites was issued on 5/28/2020, and the Office of Regulatory Affairs (ORA) attempted to schedule these inspections. However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of NDA 213498 was reevaluated. Following discussions between OSI and DN2, a decision was made that assessment of the application could proceed without GCP inspections. Therefore, at this time, OSI will be unable to determine if Protocol AC-058B301 was conducted adequately and whether the study data are reliable in support of the proposed indication.



*{See appended electronic signature page}*

Cara Alfaro, Pharm.D.  
Clinical Analyst  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Phillip Kronstein, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

cc:

Central Document Room/NDA 213498  
Division of Neurology 2/Division Director/Nicolas Kozauer  
Division of Neurology 2/Medical Officer/David Jones  
Division of Neurology 2/Team Leader/Paul Lee  
Division of Neurology 2/Project Manager/Kristen Haslam  
OSI/Office Director/David Burrow  
OSI/Office Deputy Director/Laurie Muldowney  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein  
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro  
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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CARA L ALFARO  
11/30/2020 09:47:09 AM

PHILLIP D KRONSTEIN  
11/30/2020 10:52:11 AM

KASSA AYALEW  
12/01/2020 08:29:15 AM

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LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	September 17, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 213498
Product Name and Strength:	Ponvory (Ponesimod) tablet, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc. (Janssen)
FDA Received Date:	March 18, 2020
OSE RCM #:	2020-533
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

---

## 1 REASON FOR REVIEW

As part of the approval process for Ponvory (ponesimod) tablet, the Division of Neurology 2 (DN2) requested that we review the proposed prescribing information (PI), medication guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Information Request	E
Labels and Labeling	F

N/A=not applicable for this review

\*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 PRODUCT INFORMATION

Janssen is seeking approval of Ponvory (ponesimod) tablets for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Titration is required for treatment initiation. Additionally, first-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure.

A starter pack is proposed to be used for patients initiating treatment. Treatment is initiated with a 14-day titration as follows: 2 mg once daily (Day 1 and 2), 3 mg once daily (Day 3 and 4), 4 mg once daily (Day 5 and 6), 5 mg (Day 7), 6 mg (Day 8), 7 mg (Day 9), 8 mg (Day 10), 9 mg (Day 11), 10 mg (Day 12, 13, and 14). After dose titration is complete, the recommended maintenance dosage is one 20 mg tablet once daily.

Ponvory will be supplied in the following packaging configurations: 14-day starter pack and 30-count bottle of 20 mg tablets.

#### 4 ASSESSMENT

We consulted with the Division of Neurology 2 to determine whether the proposed 14-day starter pack packaging configuration is appropriate for patients who require first dose monitoring. We inquired about the setting first dose monitoring should occur in and whether patients would be precluded from continuing on the medication if abnormalities are observed during first dose monitoring. We further inquired about whether there was any concern with the fact that other phosphate receptor modulators that require first dose monitoring (i.e., Mayzent and Gilenya) are both available in bottle configurations, whereas the starting dose of ponesimod (2 mg) is only available in the starter pack packaging configuration.

The Division advised that the expectation for ponesimod is that the initial observation (for four hours with the first dose) would have to occur in a medical setting with the potential for cardiology intervention. The primary concern with therapies like ponesimod is induction of a symptomatic bradycardia or a full cardiac conduction block. These would require expertise neurologists cannot provide. Abnormalities are rare, but if they should occur, are generally mild and should not preclude continuation of treatment depending on a physician's clinical assessment. The Division opined that a ponesimod starter pack is warranted because titration is complex. Finally, the Division was not concerned with the ponesimod starting dose (2 mg or the other doses of the complex dose titration) not being available in a bottle configuration.

We note the starter blister pack has a unique sequence concept.

(b) (4)

(b) (4)

We are concerned that the presentation of sequencing may contribute to wrong dose medication errors if it is not understood by users. For example,

(b) (4)

, both of which would result in wrong dose errors during the titration phase. We issued an Information Request to the Applicant on June 24, 2019 to clarify if they collected any usability data for use of the proposed starter pack configuration and labeling in the intended user population (See Appendix E). In their July 1, 2020 response, the Applicant states

(b) (4)

## 5 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 2			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) – General Issues			
1.	The placeholder, TRADENAME, is used throughout the PI labeling.	The proposed proprietary name, Ponvory, was found to be conditionally acceptable on August 20, 2020. <sup>a</sup>	The placeholder, TRADENAME, should be replaced with the conditionally acceptable name, Ponvory, throughout the PI labeling.
Highlights of Prescribing Information (HPI)			
1.	The Dosage and Administration Section of the HPI lacks information on route and frequency of administration.	Lacks clarity.	We recommend revising the recommended maintenance dosage statement to read: The recommended maintenance dosage is 20 mg taken orally once daily.

Table 3. Identified Issues and Recommendations for Janssen Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (Container Labels and Carton Labeling)			
1.	The labels and labeling contain the placeholder, "Tradename".	We reference our August 21, 2020 Proprietary Name Conditionally Acceptable Letter informing you that the proprietary name, Ponvory, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Ponvory, and use the intend-to-market font, color, etc.
2.	The format for expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication	Identify the expiration date format you intend to use. FDA recommends that the human-

<sup>a</sup> Morris, C. Proprietary Name Review for Ponvory (NDA 213498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 20. Panorama No. 2020-40739981.

Table 3. Identified Issues and Recommendations for Janssen Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		safety perspective (e.g., risk for deteriorated drug medication errors).	readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
General Recommendations (14-day Titration Starter Pack Packaging Configuration Design)			
1.	The starter blister pack has a unique sequence concept. (b) (4)	We are concerned that the presentation of sequencing may contribute to wrong dose medication errors if it is not understood by users. For example, (b) (4) both of which would result in wrong dose errors during the titration phase.	Ensure that potential use errors related to the blister pack sequence are evaluated in the Use-Related Risk Analysis (URRA) and validation study.
2.	(b) (4)	We find it premature to conduct a comprehensive	(b) (4)

Table 3. Identified Issues and Recommendations for Janssen Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	review of the proposed starter pack design from a medication safety and usability perspective at this time.	(b) (4)
Starter Pack Carton Labeling			
1.	It is not clear that the starter pack is a (b) (4) titration pack.	Can be improved for clarity.	Consider clarifying that the starter pack is a "14-day titration starter pack".

## 6 CONCLUSION

Our evaluation of the proposed Ponvory (ponesimod) tablet labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for DN2 and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Janssen Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.



# APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for ponesimod that Janssen Pharmaceuticals, Inc. submitted on March 18, 2020.

Table 3. Relevant Product Information for ponesimod																					
Initial Approval Date	N/A																				
Active Ingredient	ponesimod																				
Indication	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults																				
Route of Administration	Oral																				
Dosage Form	Tablet																				
Strength	2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg																				
Dose and Frequency	<p><u>Titration Initiation:</u></p> <table border="1"> <thead> <tr> <th>Titration Day</th><th>Daily Dose</th></tr> </thead> <tbody> <tr> <td>Day 1 and 2</td><td>2 mg</td></tr> <tr> <td>Day 3 and 4</td><td>3 mg</td></tr> <tr> <td>Day 5 and 6</td><td>4 mg</td></tr> <tr> <td>Day 7</td><td>5 mg</td></tr> <tr> <td>Day 8</td><td>6 mg</td></tr> <tr> <td>Day 9</td><td>7 mg</td></tr> <tr> <td>Day 10</td><td>8 mg</td></tr> <tr> <td>Day 11</td><td>9 mg</td></tr> <tr> <td>Day 12, 13 and 14</td><td>10 mg</td></tr> </tbody> </table> <p><u>Maintenance Dose:</u> 20 mg once daily</p>	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
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																				
How Supplied	<ul style="list-style-type: none"> <li>• <u>Starter Pack</u> containing 14 tablets (2x2 mg, 2x3 mg, 2x4 mg, 1x5 mg, 1x6 mg, 1x7 mg, 1x8 mg, 1x9 mg, 3x10 mg)</li> <li>• <u>Bottle</u> containing #30: 20 mg tablets</li> </ul>																				
Storage	<ul style="list-style-type: none"> <li>• <u>Starter Pack</u>: Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package.</li> <li>• <u>Bottle</u>: Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package. Do not discard desiccant. Protect from moisture.</li> </ul>																				

Container Closure	<p>Blister: (b) (4) blister (b) (4). The blister consists of a (b) (4) film (b) (4) push-through lidding film.</p> <p>Bottle: white, opaque, high density polyethylene (HDPE) 50-mL bottle with child-resistant closure and induction seal liner, containing a silica gel desiccant (2 g (b) (4))</p>
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## APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 11, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Ponesimod, NDA 213498 and IND 101722. Our search identified zero previous relevant reviews.

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## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following ponesimod labels and labeling submitted on March 18, 2020 by Janssen Pharmaceuticals, Inc..

- Container labels: Starter Pack Blister sleeve (outer wallet) and Blister Card (inner wallet) and Maintenance Dose (Bottle)
- Carton labeling: 14-day Starter Pack and Maintenance dose
- Medication Guide (Image not shown)
- Prescribing Information (Image not shown)

Refer to link in docuBridge for Prescribing Information and Medication Guide:

[\\cdsesub1\evsprod\nda213498\0001\m1\us\annotated-draft-labeling-text.pdf](#)

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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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BRIANA B RIDER  
09/18/2020 09:14:56 AM