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MAR 29 2019

Re: Docket No. FDA-2018-P-4490

Dear Ms. Livornese:

This letter responds to the citizen petition you submitted to the Food and Drug Administration (FDA or the Agency) on behalf of Hyman, Phelps & McNamara, P.C., received on November 21, 2018 (Petition). In the Petition, you request that FDA refrain from approving any supplemental new drug application (sNDA) for Zelnorm (tegaserod maleate) unless the sNDA contains substantial evidence of safety and effectiveness for the proposed use in the proposed population under current applicable standards. In the alternative, if FDA approves an sNDA for Zelnorm, the Petition requests that:

- FDA include postmarketing obligations for the sponsor to conduct new randomized placebo-controlled clinical trials in accordance with the standards identified in relevant FDA guidance
- The labeling for the product be revised and updated to include, among other things, appropriate statements alerting prescribers that effectiveness has not been demonstrated to current standards in the indicated population
- The sponsor implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh its risks by making prescribers aware of important limitations of its use and differences in the new approval compared to the old approval and compared to current standards

We have carefully considered the Petition and all comments submitted to the docket. For the reasons discussed below, your Petition is denied.

I. BACKGROUND

A. Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain and change in bowel habits. Clinical manifestations may include cramping, bloating, abdominal distention, flatulence, mucus in stool, and urgency of bowel movements. IBS is classified into four subtypes depending on the predominant change in bowel habits: constipation (IBS-C), diarrhea (IBC-D), mixed (IBS-M), and

unclassified.[1]

The pathophysiology of IBS is not definitively known; it is multifactorial and underlying causes may vary among different patients. Traditionally, IBS was thought to be primarily due to visceral hypersensitivity and GI motor disturbances. More recently, there is increasing evidence for the contributing factors of infection, immune activation, serotonin dysregulation, bacterial overgrowth, central dysregulation and brain-gut interaction, and genetics. Although clinical presentations vary, many patients with IBS have chronic symptoms with fluctuating severity and episodic flares. IBS can impact quality of life, having both predictable and unpredictable triggers. Some patients with IBS tolerate their symptoms well with minimal impairment in daily functioning, while other patients have symptoms that prevent them from working or participating in usual activities.[2]

Multiple treatment options with varying mechanisms of action are needed for patients with IBS-C. Because causes and clinical presentations vary among patients with IBS-C, treatment for this condition is individualized and focuses on symptom relief. Treatment may include dietary and lifestyle modification and/or pharmacologic agents (prescription or over-the-counter). The available treatment options do not completely meet the needs of patients with IBS-C; the FDA-approved prescription drug products have modest benefit over placebo, and over-the-counter and nondrug therapies are not specifically approved for IBS-C.[3]

B. Zelnorm

Today, FDA approved sNDA 015 under new drug application (NDA) 021200 for Zelnorm submitted by Sloan Pharma S.a.r.l, Bertrange, Cham Branch (Sloan) through its U.S. agent US WorldMeds, LLC (collectively, Applicant) for the treatment of adult women less than 65 years of age with IBS-C. The relevant regulatory history for this application is summarized below.[4]

1. Mechanism of Action

Zelnorm is a serotonin type 4 (5-HT_4) receptor agonist that binds with high affinity at human 5-HT_4 receptors, and with moderate to high affinities for 5-HT_1 and 5-HT_2 receptor subtypes. Investigations suggest an important role of 5-HT_4 receptors in the maintenance of GI functions in humans. 5-HT_4 receptor mRNA has been found throughout the human GI tract. The activation of 5-HT_4 receptors in the GI tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity.[5]

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[1] See Multi-Discipline Review for Zelnorm at 20, available on FDA's webpage at https://www.accessdata.fda.gov/scripts/cder/daf/ (Multi-Discipline Review for Zelnorm).
[2] Id.
[3] Id. at 5.
[4] For a detailed discussion about the regulatory and approval history for Zelnorm, see Multi-Discipline Review for Zelnorm.
[5] Id. at 7.

2. *Original 2002 Zelnorm Approval*

On July 24, 2002, FDA approved NDA 021200 for Zelnorm for the short-term treatment of women with IBS whose primary bowl symptom is constipation.[6] Zelnorm was the first drug approved to treat IBS-C.[7] The Zelnorm NDA was supported by three phase 3 randomized, double-blind, placebo-controlled, multicenter trials to assess the drug's safety and efficacy: trials 301, 307, and 358.[8] The trial design for all three trials was generally similar and consisted of a 4-week baseline period followed by a 12-week double-blind treatment period. Trial 358 had an additional 1-month withdrawal period to allow assessment of any change in IBS symptoms after completing the treatment period.

All three trials included as their primary endpoint the proportion of patients who achieve a threshold improvement in the Subject Global Assessment of Relief (SGA), a patient-reported outcome measure of IBS-related symptom change and overall well-being.[9] Although, at month 3, only trial 301 achieved statistical significance on the primary endpoint at the 0.05 level, with a treatment difference of 11% (95% CI, 3% to 20%), trial 358 provided evidence of efficacy with a treatment difference of 5% (95% CI, 0% to 10%). Trial 307 had a treatment difference of 5% (95% CI, -4% to 14%) that was not statistically significant. Based on the collective evidence from all three trials, the Agency determined that Zelnorm is efficacious for the treatment of IBS-C in women.[10]

3. *Zelnorm Removal From U.S. Market*

In 2007, Novartis Pharmaceuticals Corporation (Novartis), the sponsor for Zelnorm at the time, notified FDA that a preliminary retrospective analysis of pooled clinical trial data suggested an imbalance in cardiovascular (CV) ischemic adverse events with Zelnorm that had not been previously identified.[11] On March 9, 2007, Novartis provided a comprehensive analysis of the data, which was discussed during a March 15, 2007, Type

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[6] On August 21, 2004, FDA approved a new indication for Zelnorm for the treatment of patients under 65 years of age with chronic idiopathic constipation. The Applicant is not seeking to reintroduce Zelnorm for this indication.

[7] Since Zelnorm was removed from the U.S. market, FDA approved three new treatments for IBS-C, each with a mechanism of action different from Zelnorm. First, Amitiza (lubiprostone) (approved by FDA for IBS-C in 2008) is a chloride channel activator, which increases intestinal fluid secretion and results in increased motility in the intestine. Second, Linzess (linaclotide) (approved by FDA for IBS-C in 2012) is a guanylate cyclase-C agonist, which results in increased intestinal fluid and accelerated transit. Finally, Trulance (plecanatide) (approved by FDA for IBS-C in 2018) is also a guanylate cyclase-C agonist. See Multi-Discipline Review for Zelnorm at 21-22.

[8] See Multi-Discipline Review for Zelnorm at 29. The sponsor also submitted a fourth trial (351), which was considered exploratory because the primary endpoint for trials 301, 307, and 358 was used in a post hoc analysis for trial 351. Though trial 351 provided supportive evidence of benefit, it was not included in the original labeling.

[9] See Multi-Discipline Review for Zelnorm at 31.

[10] Id. at 32-33.

[11] Id. at 5.

A meeting. During this meeting, Novartis expressed its intent to conduct additional external adjudications of the suspect CV cases with more source information on baseline CV disease severity and an epidemiologic study. On March 23, 2007, Novartis submitted the results of the first external adjudication of suspect CV cases by a panel of experts at Mt. Sinai Medical Center.[12] This adjudication of the reported CV ischemic events identified an imbalance in patients taking Zelnorm (13 events, 0.1%) compared to placebo (1 event, 0.01%), and 7 major adverse cardiac events (0.06%) (MACE, a subset of CV ischemic events) on Zelnorm compared to none on placebo.[13] On March 27, 2007, FDA convened a center-level briefing to discuss the Zelnorm risk assessment. Following that discussion, FDA held a meeting with Novartis on March 28, 2007, where FDA asked Novartis to voluntarily remove Zelnorm due to safety concerns with the drug. On March 29, 2007, Novartis informed FDA that it would immediately suspend marketing and sales of Zelnorm and voluntarily remove the product from the pipeline.[14]

4. Post-Removal Activity

During the March 28, 2007 meeting, FDA agreed that after removal of Zelnorm from the U.S. market, FDA would continue to work with Novartis to identify an appropriate target population in whom the benefits of Zelnorm would outweigh its risks. After removing Zelnorm from the U.S. market, Novartis submitted a second external adjudication report dated February 1, 2008, conducted by Duke Clinical Research Institute. This analysis included additional information to document events, timing, co-administered drugs, and any significant studies to diagnose CV ischemia among the suspected cases.[15] This second adjudication confirmed 7 CV ischemic events (0.06%) on Zelnorm compared to 1 event (0.01%) on placebo, and 4 MACE events (0.03%) on Zelnorm compared to none on placebo.[16]

Also following removal of Zelnorm, several meetings occurred between FDA and Novartis about reintroducing Zelnorm to the U.S. market. The NDA for Zelnorm was transferred to Sloan effective November 24, 2015, and FDA continued these discussions with the Applicant. During these discussions, FDA recommended that the Applicant focus its reintroduction efforts on the IBS-C population and identify a subpopulation of patients for which the benefits of Zelnorm would outweigh any CV risks.[17]

5. Supplemental NDA To Reintroduce Zelnorm to the U.S. Market

On February 26, 2018, the Applicant submitted an sNDA to reintroduce Zelnorm to the U.S. market.[18] The Applicant proposed an indication for the treatment of women with IBS-C less than 65 years of age, with contraindications relating to CV safety as follows:

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[12] See Multi-Discipline Review for Zelnorm at 23.
[13] Id. at 86.
[14] Id. at 24. Soon after removal, Zelnorm became available through an expanded access program.
[15] Id.
[16] Id. at 60.
[17] Id. at 25.
[18] Id. at 26.

- A history of CV ischemic disease, such as myocardial infarction (MI), stroke, transient ischemic attack (TIA), or angina
- More than one CV risk factor: hypertension, tobacco use, diabetes, hypercholesterolemia, age at or greater than 55, and obesity

During FDA's review of the sNDA, the Applicant proposed to narrow the contraindication to only those with a history of CV ischemic disease.

To the support the safety and effectiveness of Zelnorm under sNDA 015, the Applicant included the following data:

- Data from original Zelnorm 12-week trials (301, 307, and 358) for the primary efficacy analyses
- Data from 4-week post approval trials (2306, 2417)
- Efficacy datasets from study 351
- A safety database (Db15) consisting of 29 placebo-controlled trials of at least 4 weeks duration
- Additional safety evidence from epidemiological study findings, nonclinical data, pharmacology studies including platelet aggregation data, and an analysis of postmarketing observational data[19]

At FDA's request, the Applicant also defined a subgroup of "severely symptomatic" IBS-C patients and included additional post hoc efficacy analyses from the original Zelnorm clinical trial data in this subgroup.[20] Given the potential CV safety signal prompting removal of Zelnorm from the market, FDA determined that an advisory committee should review and provide expert input on the data submitted to support sNDA 015 for Zelnorm.

6. *October 17, 2018, Gastrointestinal Drugs Advisory Committee Meeting*

On October 17, 2018, FDA convened the Gastrointestinal Drugs Advisory Committee (GIDAC) to address discussion questions regarding the safety and effectiveness of Zelnorm for reintroduction to the U.S. market.[21] Of relevance, the GIDAC was asked to address the following:

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[19] See Multi-Discipline Review for Zelnorm at 9-12.

[20] Id. at 25-26. FDA requested these analyses in case a more restricted population was deemed necessary to balance the benefits and risks of Zelnorm after appropriate review and presentation before an advisory committee. As discussed below, FDA ultimately determined that Zelnorm use should not be restricted to a severely symptomatic population.

[21] A copy of the briefing materials and summary minutes of the meeting are available on FDA's webpage at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm593142.htm.

- The strength of the potential CV safety signal of Zelnorm, considering the totality of the available data from clinical trials, case adjudications, pharmacoepidemiology studies, nonclinical data, and pharmacovigilance
- Whether the therapeutic gain (treatment difference between Zelnorm and placebo patients) is generally similar in magnitude between the severely symptomatic and originally approved population
- The population in which they would expect the benefits of Zelnorm to outweigh its risks: IBS-C females, IBS-C females at low CV risk, IBS-C females who are severely symptomatic, IBS-C females at low CV risk and who are severely symptomatic, or other
- Whether the reintroduction of Zelnorm to the U.S. market is supported by the available safety data [22]

The majority of the GIDAC agreed that although a CV safety signal may exist for Zelnorm, the overall strength of the signal is weak, if present at all.[23] Nonetheless, the GIDAC was concerned about possible CV events with use of the drug in a broader patient population and therefore the majority of committee members voted in favor of reintroducing Zelnorm in a population of IBS-C females at low CV risk.[24] Notably, 11 out of the 12 GIDAC members agreed that reintroduction of Zelnorm to the U.S. market was supported by the available safety and efficacy data. The GIDAC members noted that the clinical trial data showed that Zelnorm is effective in the treatment of IBS-C and that the weak CV safety signal could be properly addressed through labeling.

No members recommended that the approved indication for Zelnorm should be limited to IBS-C females who are severely symptomatic, and only three members recommended that the indication be limited to IBS-C female patients at low CV risk and who are severely symptomatic.[25] Following the GIDAC meeting, and after considering the collective data submitted to support the Zelnorm sNDA, FDA decided that the indication for Zelnorm should not be restricted to more severely affected patients for several reasons, including lack of established clinical guidelines for "severe" symptoms, the fluctuating nature of disease symptoms, and a weak signal for CV events associated with Zelnorm use.[26] In light of that decision, we need not address your questions about the appropriateness of an indication for a severely symptomatic IBS-C population.

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[22] See Summary Minutes of the Gastrointestinal Drugs Advisory Committee, October 17, 2018 (GIDAC Meeting Minutes), at 5-6, available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM626241.pdf. FDA also asked the GIDAC to discuss other potential safety concerns not relevant to the Petition's requests, including psychiatric safety adverse events of completed suicide and suicidal ideation/behavior.

[23] See GIDAC Meeting Minutes at 5.

[24] Id. at 6.

[25] Id. at 6.

[26] See Multi-Discipline Review for Zelnorm at 35-36.

7. *2019 Zelnorm Approval*

Following the GIDAC's advice, FDA considered how to define a population at low CV risk. Because increasing age is a known independent risk factor for cardiovascular disease, limiting the Zelnorm indication for use in adult women with IBS-C under age 65 is one effective way to minimize cardiovascular risk. In identifying clinical circumstances where Zelnorm use should be contraindicated, FDA determined that a history of CV ischemic disease without including additional CV risk factors was clinically warranted.[27] Specifically, manifestations of CV ischemic disease (i.e., MI, stroke, TIA, or angina) are well-known objective indicators of a higher CV risk that can be easily identified in clinical practice. Consistent with FDA labeling regulations and policy,[28] a history of CV ischemic disease is included in the CONTRAINDICATIONS section of the Zelnorm labeling.[29]

A patient population with the CV risk factors identified by the Applicant is more complex to define operationally. For example, hypertension can be well-controlled or poorly-controlled, and the CV risk is likely different in these groups. Moreover, 99% of subjects evaluated in Db15 with more than one identified CV risk factor did not have a CV event. Contraindicating the drug for patients with more than one CV risk factor therefore may unduly restrict access for those patients who might benefit from the drug. Data to inform a discussion between a prescriber and patient about the relevance of CV risk factors when prescribing Zelnorm are included in other sections of the Zelnorm approved labeling, including section 5 (WARNINGS AND PRECAUTIONS), section 6 (ADVERSE REACTIONS), section 17 (PATIENT COUNSELING INFORMATION), and in the patient Medication Guide.

Regarding effectiveness in the indicated population, the trials supporting Zelnorm's original approval provided substantial evidence of effectiveness for the population of adult women with IBS-C. In its review of the sNDA, FDA conducted additional post hoc analyses in the subgroup of adult women with IBS-C under age 65 to determine whether treatment effects were comparable to those in the original population.

Notably, treatment differences at 1 month and 3 months of Zelnorm use were generally similar between adult female patients with IBS-C at low CV risk (defined as age less than 65; range 4% to 16%) and the originally indicated (overall) population of adult female patients with IBS-C (range 5% to 14%) (See II.A.1, below).[30]

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[27] Id. at 10.

[28] See § 201.57 (21 CFR 201.57) and draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2018). When final, this guidance will represent FDA's current thinking on this topic. We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/.

[29] See FDA-approved labeling for Zelnorm at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[30] See Multi-Discipline Review for Zelnorm at 16. Although the Petition claims (at 7) that the "modest" size of the Zelnorm treatment effect should not be ignored for the sNDA review, FDA does not believe that

Based on the totality of the data submitted to support the Zelnorm sNDA, FDA determined that the sNDA meets applicable scientific and legal standards for approval and that the benefits of Zelnorm outweigh its risks when used in accordance with its FDA-approved labeling.

C. Statutory and Regulatory Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a sponsor seeking to market a new drug submit an NDA to FDA for review.[31] To be approved, an NDA submitted under section 505(b) of the FD&C Act (21 U.S.C.355(b)) must, among other things, be supported by investigations showing the drug product to be safe and effective for its intended use(s).[32] Section 505(c)(1)(A) of the FD&C Act states that FDA shall "approve the application if [FDA] . . . finds that none of the grounds for denying approval specified in [section 505(d) of the FD&C Act] applies." Section 505(d) of the FD&C Act and FDA's regulation at 21 CFR 314.125(b) include grounds for refusing to approve an application. For example, FDA shall refuse to approve an application if adequate tests do not show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. FDA shall also refuse to approve an application if the applicant fails to provide substantial evidence of effectiveness. As stated in section 505(d) of the FD&C Act, "substantial evidence" means:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

At least two adequate and well-controlled studies, each convincing on its own, are generally required to establish substantial evidence of effectiveness. The characteristics of adequate and well-controlled clinical investigations are described in FDA's regulation at 21 CFR 314.126. FDA's guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) outlines the Agency's current thinking on acceptable approaches to meeting these statutory and regulatory requirements.[33]

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the treatment effect, already determined to be clinically meaningful, should be revisited here. FDA routinely approves drugs across a magnitude of treatment effects. Even small treatment effects could be clinically meaningful for patients. Moreover, the treatment effects for all FDA-approved drugs to treat IBS-C can generally be described as "modest."

[31] Section 505(a) of the FD&C Act and part 314 (21 CFR part 314).

[32] Section 505(b)(1) of the FD&C Act.

[33] Available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment. That assessment "takes into account the extensive evidence of safety and effectiveness submitted by a sponsor . . . as well as many other factors affecting the benefit-risk assessment . . . . This assessment involves both quantitative analyses and a subjective qualitative weighing of evidence."[34] Key considerations of benefit "[i]nclude the results of the clinical trials and the clinical meaning of primary and secondary endpoints, as well as appropriate analyses of subpopulations."[35] Key considerations of risk "[i]nclude the adequacy of the safety database, the severity and reversibility of adverse events, and the potential for sub-optimal management in the post-market setting that may be of concern."[36]

II. DISCUSSION

A. The Applicant Has Provided Substantial Evidence of Effectiveness and Positive Benefit-Risk Profile for Zelnorm

1. The Data Supporting sNDA 015 Are Sufficient To Establish a Benefit for Zelnorm in the Indicated Population

The Petition claims that the Applicant is required to demonstrate safety and effectiveness of the drug specifically in the subgroup for which the drug is indicated, but no data from clinical trials designed to evaluate the effectiveness in this subgroup have been submitted in the Zelnorm sNDA.[37] The Petition also claims that the Applicant's reliance on the original trials cannot be used to define a benefit as part of the benefit-risk assessment for Zelnorm in IBS-C women with low CV risk.[38] The Agency disagrees.

In 2002, FDA concluded that the clinical trials submitted to support the Zelnorm approval demonstrated substantial evidence of effectiveness. Having established effectiveness in the overall population of adult women with IBS-C, for this review, the Agency conducted additional post hoc analyses to determine whether the effects in the subgroup of adult women with IBS-C under 65 were comparable.[39] Across the three Zelnorm pivotal trials (301, 307, 358), 94% percent of women were under the age of 65.[40] As such, FDA did not expect substantial differences between the overall and narrowed populations. Indeed,

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[34] See *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making, Draft PDUFA V Implementation Plan—February 2013, Fiscal Years 2013-2017*, at 1, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.

[35] Id. at 6.

[36] Id.

[37] Petition at 5-6.

[38] Id.

[39] See Multi-Discipline Review for Zelnorm at 33.

[40] The narrowed population remained 94% of the original population when considering trial (351). Although trial 351 was considered exploratory for the Zelnorm original approval, FDA included trial 351 in the analyses to support the sNDA approval because the same primary endpoint was being evaluated in a post hoc nature for all trials and there did not appear to be any data integrity concerns that would preclude the data from these analyses. See Multi-Discipline Review for Zelnorm at 29.

as shown in Table 1, the subgroup analyses confirmed that the benefit to the narrowed population is comparable to that in the overall population.

Table 1: Primary Efficacy Responder* Rate in Adult Females with IBS-C <65 Years of Age

	Females < 65 Years of Age			Original Approval Treatment Difference in All Female Subjects with IBS-C 95% CI (%)
Study ID	Tegaserod 6 mg Twice Daily n/N (%)	Placebo n/N (%)	Percent Difference in Response (95% CI)	
			Month 1	
301	73/220 (33)	38/217 (18)	16 (8, 24)	14 (6, 21)
307	73/210 (35)	44/213 (21)	14 (6, 23)	14 (6, 22)
358	260/744 (35)	158/725 (22)	13 (9, 18)	13 (8, 17)
351	78 / 221 (35)	52 / 219 (24)	12 (3, 20)	9 (0, 17)
			Month 3**	
301	90 / 220 (41)	61 / 217 (28)	13 (5, 22)	11 (3, 20)
307	91 / 210 (43)	84 / 213 (39)	4 (-5, 13)	5 (-4, 14)
358	327 / 744 (44)	283 / 725 (39)	5 (0, 10)	5 (0, 10)
351	107 / 221 (48)	73 / 219 (33)	15 (6, 24)	14 (6, 23)

*A responder at Month 1 is defined as a patient with ≥ 2 of 4 weeks with complete or considerable relief, or 4 of 4 weeks with at least somewhat relief on the subject global assessment during the first 4 weeks; a responder at Month 3 is defined as a patient with ≥ 2 of 4 weeks with complete or considerable relief, or 4 of 4 weeks with at least somewhat relief during the last 4 weeks with available diary records.
**Primary efficacy assessment.
Abbreviations: CI, confidence interval

FDA also conducted post hoc subgroup analyses in the indicated population of adult women with IBS-C under 65 years of age, removing those patients with a history of CV ischemic disease for which the drug is contraindicated. Notably, only 17 patients in the original Zelnorm trials had a history of CV ischemic disease and this narrowed subgroup remained 94% of the overall population.[41] As shown in Table 2, efficacy results in this subpopulation were also consistent with the results in the overall population.

[41] Patient medical histories were collected in the original clinical trials as specified in the protocols, and relevant CV status was screened retrospectively for this review to identify patients with a history of a CV ischemic event. Although a CV ischemic event may not be reflected in the patient's record if, for example, the patient did not report it, the Agency believes that important CV events are generally collected for patients when enrolled in clinical trials. As such, we do not expect significant missing data for CV ischemic events.

Table 2: Primary Efficacy Responder* Rate in Adult Females with IBS-C <65 Years of Age With No Cardiovascular Ischemic Disease History at Baseline

	Females < 65 Years of Age With No CVI History at Baseline			Original Approval Treatment Difference in All Female Subjects with IBS-C 95% CI (%)
Study ID	Tegaserod 6 mg Twice Daily n/N (%)	Placebo n/N (%)	Percent Difference in Response (95% CI)	
			Month 1	
301	73 / 219 (33)	38 / 217 (18)	16 (8, 24)	14 (6, 21)
307	72 / 209 (34)	44 / 212 (21)	14 (5, 23)	14 (6, 22)
358	256 / 738 (35)	157 / 719 (22)	13 (8, 17)	13 (8, 17)
351	78 / 220 (36)	52 / 218 (24)	12 (3, 20)	9 (0, 17)
			Month 3**	
301	89 / 219 (41)	61 / 217 (28)	13 (4, 22)	11 (3, 20)
307	91 / 209 (44)	83 / 212 (39)	5 (-5, 14)	5 (-4, 14)
358	324 / 738 (44)	282 / 719 (39)	5 (0, 10)	5 (0, 10)
351	107 / 220 (49)	73 / 218 (34)	15 (6, 24)	14 (6, 23)

*A responder at Month 1 is defined as a patient with ≥ 2 of 4 weeks with complete or considerable relief, or 4 of 4 weeks with at least somewhat relief on the subject global assessment during the first 4 weeks; a responder at Month 3 is defined as a patient with ≥ 2 of 4 weeks with complete or considerable relief, or 4 of 4 weeks with at least somewhat relief during the last 4 weeks with available diary records.
**Primary efficacy assessment.
Abbreviations: CI, confidence interval

The results of these two analyses are consistent with our mechanistic understanding that risk of CV disease or a history of CV events would not be expected to impact the efficacy of Zelnorm. The Agency is not aware of any clinical or biological mechanism where risk or history of CV disease should affect a patient's response to Zelnorm. Zelnorm is a 5-HT_4 receptor agonist that binds with high affinity at human 5-HT_4 receptors. Although the presence of 5-HT_4 receptors in the heart raises concern about possible off-target CV events, this would not impact the efficacy of the drug in the GI tract. The Petition presents no evidence to the contrary.

The totality of the data support that the Applicant has demonstrated substantial evidence of effectiveness and that the benefits of Zelnorm for the indicated population outweigh its risks when used in accordance with its FDA-approved labeling.[42]

2. *Reanalysis of the Zelnorm Original Data Is Appropriate To Describe Subgroup Effects*

The Petition claims that a post hoc analysis of subgroup data from the clinical trials that supported the original Zelnorm approval is not adequate to support approval of the

[42] For a more detailed discussion about the efficacy review for Zelnorm, see Multi-Discipline Review for Zelnorm at 29-36.

sNDA.[43] To support that claim, the Petition quotes from FDA's draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017) (Multiple Endpoints draft guidance)[44] as confirmation that the Zelnorm post hoc analyses cannot inform effectiveness here.[45] The guidance states:

> Although post hoc analyses of trials that fail on their prospectively specified endpoints may be useful for generating hypotheses for future testing, they do not yield definitive results. The results of such analyses can be biased because the choice of analyses can be influenced by a desire for success. The results also represent a multiplicity problem because there is no way to know how many different analyses were performed and there is no credible way to correct for the multiplicity of the statistical analyses and control the Type I error rate. Consequently, post hoc analyses by themselves cannot establish effectiveness.[46]

The guidance is referring to post hoc analysis of trials that fail on their prospectively specified endpoints where multiple different subpopulations are subsequently analyzed without multiplicity adjustment to find a population for which effectiveness can be demonstrated. Contrary to the Petition's assertion, the post hoc analyses conducted to support the Zelnorm sNDA do not fit this category.

For the Zelnorm original approval, substantial evidence of effectiveness was already demonstrated in the overall study population. Here, to address a safety signal, the indicated population has been narrowed to adult women with IBS-C under the age of 65. Although the narrowed population was not specified in advance, this is not a case as described above where multiplicity is of concern. Therefore, FDA determined that post hoc analyses characterizing whether the treatment effect was similar in the narrowed population were appropriate. As described above, efficacy results in the narrowed indicated population (which constitutes almost the entire overall population of women) were consistent with the treatment effect in the overall population.

3. *The Availability of Other FDA-Approved Treatments for IBS-C Does Not Negate the Positive Benefit-Risk Profile for Zelnorm*

The Petition claims that because FDA approved more drugs to treat IBS-C after Zelnorm was removed from the market, "it is even more important that the sNDA demonstrates a positive risk-benefit profile than was the case when it was originally approved."[47] Although the availability of current treatment options is a factor considered in the benefit-risk assessment to provide context for weighing the benefits and risks of a drug, including unmet needs, FDA is satisfied that the data supporting the Zelnorm sNDA

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[43] Petition at 8.

[44] A copy of the draft guidance is available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536750.pdf. When final, this guidance will represent FDA's current thinking on this topic.

[45] Petition at 8.

[46] See Multiple Endpoints draft guidance at 8.

[47] Petition at 15.

demonstrates a positive benefit-risk profile when the drug is used in accordance with its FDA-approved labeling (see section II.A.1 above).[48]

IBS-C is a complicated disorder to manage and the pathophysiology underlying IBS-C is likely multifactorial. The current FDA-approved treatment options for IBS-C (i.e., lubiprostone, linaclotide, and plecanatide) are primarily prosecretory, whereas Zelnorm offers a different mechanism of action,[49] primarily by stimulating colonic peristalsis. As described above, not all patients with IBS-C will have an adequate response to therapy and additional safe and effective treatment options with varying mechanisms of action are needed. FDA considers patient access to a variety of safe and effective treatment options beneficial to public health. FDA routinely approves multiple drugs in a class or for a specific indication that may have different dosage forms, routes of administration, formulations, and benefits and risks, provided the benefits of each drug outweigh its risks.

4. The Effectiveness Data Supporting the Original Zelnorm Approval Remain Clinically Meaningful and Relevant

After Zelnorm was removed from the market, FDA issued a guidance for industry titled *Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment* (May 2012) (2012 IBS Guidance) providing recommendations to stakeholders about drug development programs for IBS drugs.[50] The Petition claims that differences between the Zelnorm development program and recommendations in the 2012 IBS Guidance should limit reintroducing Zelnorm to the market or proscribe its use.[51] The Agency does not agree.

FDA acknowledges that the primary efficacy endpoint used in the original Zelnorm trials based on the SGA is no longer recommended in the 2012 IBS Guidance. Instead, FDA recommends a primary endpoint for IBS-C based on abdominal pain and stool frequency and that a secondary endpoint could be based on abdominal discomfort.[52] However, the secondary endpoints included in the Zelnorm trials evaluated the effect of Zelnorm on core IBS-C signs and symptoms, including relief of abdominal pain/discomfort[53] and

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[48] See Benefit-Risk Assessment in Drug Regulatory Decision-Marking, Draft PDUFA VI Implementation Plan (FY 2018-2022), available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf.

[49] The Petition claims (at 15) that although the mechanism of action for Zelnorm may provide unique relief for some patients, that patient group appears to be small based on the small number of patients testifying at the GIDAC. FDA does not believe it can draw any conclusion about the number of patients for whom Zelnorm may provide benefits based on the number of patients testifying at the GIDAC. It is unlikely that most patients were aware of the GIDAC meeting or would volunteer to testify.

[50] A copy of the guidance is available at https://www.fda.gov/RegulatoryInformation/Guidances/.

[51] Petition at 10-13.

[52] See 2012 IBS Guidance at 5.

[53] As recognized in the 2012 IBS Guidance, it remains unclear whether patients distinguish between these two symptoms. Although the Petition states (at 12) that prescribers are likely to believe that the current Zelnorm approval means that the drug was found to be safe and effective under the "standards" in the 2012 IBS Guidance (e.g., reducing pain), the approved Zelnorm labeling uses the terminology "pain/discomfort"

stool frequency. The clinical benefit for these symptoms are described in the Zelnorm labeling.[54] Therefore, the core signs and symptoms of IBS-C currently recommended for analysis as primary and secondary endpoints were collected and evaluated in the original Zelnorm trials and continue to be clinically meaningful and relevant for IBS-C patients.

The Petition also claims that the scientific understanding of what constitutes a clinically meaningful benefit to IBS-C sufferers has grown, as indicated by the change in the diagnostic criteria issued by the Rome Foundation since the original Zelnorm approval.[55] Although the Rome criteria have been amended since the original Zelnorm approval (Rome II), we do not believe that those changes impact the approvability of Zelnorm or decrease the clinical relevance of the data collected in the original Zelnorm trials. The changes between Rome II, Rome III, and Rome IV mainly reflect differences in characterizing IBS subtypes. Specifically, the Rome II criteria (1999) did not include IBS subtypes based on stool consistency, whereas Rome III criteria (2006) did. Rome III also removed bloating as a diagnostic criterion because it is common with gastrointestinal disorders and not specific for IBS, though approximately 80% of patients with IBS, particularly IBS-C, report bloating[56] as the second most bothersome symptom after abdominal cramping/discomfort/pain.[57]

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to reflect the data as collected in the clinical trials. Therefore, prescribers should not be confused or misinterpret what was measured in those trials.

[54] See FDA approved labeling for Zelnorm at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Specifically, regarding these core symptoms and bloating (another symptom measured in the trials), the FDA-approved labeling for Zelnorm states:

> During the first four weeks in the fixed dose trials, 8 to 11% more ZELNORM-treated patients than placebo-treated patients were responders for abdominal pain/discomfort. Similarly, 9 to 12% more ZELNORM-treated patients were responders for bloating. Corresponding differences at month 3 were 1 to 10% responders for abdominal pain/discomfort and 4 to 11% responders for bloating. Patients on ZELNORM also experienced an increase in median number of bowel movements from 3.8/week at baseline to 6.3/week at month 1 and 6.0/week at month 3, while placebo patients increased from 4.0/week to 5.1/week at month 1 and 5.5/week at month 3.

As described above, because the narrowed population of women under 65 years of age with IBS-C comprises 94% of the overall population, and the post hoc analyses confirmed comparable treatment effects on the primary endpoint, the Agency does not expect any significant differences in these measured symptoms between the narrowed and overall population.

[55] Petition at 10.

[56] The Petition claims (at 14) that the Clinical Studies section of the Zelnorm labeling should not include information on bloating unless and until bloating is assessed by a clinical trial meeting a bloating endpoint that is based on evidence collected employing "current methods of assessment." However, the Petition does not cite any "current methods of assessment" under which it believes bloating should be measured. The Agency acknowledges the challenges in characterizing bloating operationally. However, as stated above, 80% of IBS-C patients report bloating as a significantly bothersome clinical symptom and the approved Zelnorm labeling accurately describes the impact on bloating as measured in the clinical trials. As such, the Agency declines to remove bloating from the labeling in this case.

[57] See Ringel, Y., at al. Prevalance, Characteristics, and Impact of Bloating Symptoms in Patients with Irritable Bowel Syndrome. Clin Gastroenterol Hepatol 2009;7:68-72.

Rome IV criteria (2016) removed reference to "discomfort" because some languages do not have a translation for that term and because it is unclear whether patients distinguish pain from discomfort. Notably, Rome II was used as the diagnostic criteria for enrollment into the trials that supported approval of linaclotide and lubiprostone, and Rome III was used for plecanatide. Both Rome II and III include discomfort or pain as diagnostic criteria. Diagnostic criteria used in the Zelnorm trials are therefore consistent with other FDA-approved drugs to treat IBS-C.[58]

5. A Postmarketing Effectiveness Study for Zelnorm Is Not Warranted

The Petition requests that if FDA approves the Zelnorm sNDA, FDA should require a postmarketing requirement (PMR) for the Applicant to conduct and complete within 24 months a confirmatory efficacy study following the 2012 IBS Guidance to determine whether the drug is effective as a second line treatment for the approved patient population under current standards.[59] The Agency does not believe that a PMR is warranted here. First, the Petition presents no data to justify studying Zelnorm as a second-line treatment and Zelnorm has not been limited as a second-line treatment. Second, as described above, the efficacy data submitted to support the Zelnorm original approval remain clinically meaningful and relevant to adult women with IBS-C and subgroup analyses support efficacy in the indicated population of adult women with IBS-C under 65 years of age.

Given these factors, requiring the Applicant to conduct additional clinical trials is not necessary.

B. Labeling Alone Is Sufficient To Communicate the Relevant Benefits and Risks Associated With Zelnorm

1. The Zelnorm Approved Labeling Appropriately Characterizes the Clinical Evidence of Effectiveness

The Petition claims that if Zelnorm is approved, the labeling will not meet the regulatory requirement that it include adequate directions for use under 21 CFR 201.100(c)(1) unless the prescribing information includes explanations of the limitations of evidence on which its approval is based (e.g., not according with the recommendations in the 2012 IBS Guidance) and such limitations should be included in the INDICATIONS AND

[58] Moreover, the import of the diagnostic criteria in a clinical trial is to determine whether, in combination with other eligibility criteria, the Zelnorm trials included an appropriate patient population to evaluate the benefits and risks of the drug for the indicated population. The clinical trial enrollment criteria in the Zelnorm trials accounted for the IBS-C subtype, and patients enrolled in the clinical trials were required to have at least a 3-month history of IBS symptoms before the study baseline period that included abdominal pain and constipation. See Multi-Discipline Review for Zelnorm at 14. Therefore, the major distinction between Rome II and updated criteria—accounting for IBS subtypes—were appropriately addressed by the clinical trial enrollment criteria.

[59] Petition at 14.

USAGE section of the approved labeling.[60] FDA does not agree that the evidence supporting the Zelnorm sNDA is limited or requires a limitation of use in the INDICATIONS AND USAGE section.

As described in FDA's draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drugs and Biological Products — Content and Format* (July 2018) (Labeling Guidance),[61] "[a] limitation of use is included when there is reasonable concern or uncertainty among FDA's expert reviewers, who are qualified by scientific training and experience, about a drug's risk-benefit profile."[62] For the reasons described above, FDA has no reasonable concern or uncertainty about Zelnorm's risk-benefit profile that would warrant a limitation of use at this time.

Additionally, clinical understanding of diseases and symptoms evolve over time and different drugs approved for the same indication may use different endpoints and analyses to support approval. [63] As such, FDA-approved labeling includes in section 14 (CLINICAL STUDIES) a description of the clinical studies supporting a product's approval, including endpoints evaluated. The Agency believes that the FDA-approved labeling for Zelnorm accurately describes the clinical evidence of effectiveness, including the trial design, endpoints, and results that were evaluated in the Zelnorm clinical trials. This information, in conjunction with other parts of the labeling, provides prescribers with adequate and accurate information to consider whether Zelnorm is appropriate for a given patient.

2. *A Risk Evaluation and Mitigation Strategy for Zelnorm Is Not Warranted*

The Petition claims that if FDA approves the Zelnorm sNDA, FDA should require the sponsor to implement a Risk Evaluation and Mitigation Strategy (REMS) because both patients and prescribers are likely to assume that the indication and limitations on use are the same as when Zelnorm was removed from the market.[64] The Petition notes that a REMS could take many forms but should include, at a minimum, a plan to inform healthcare providers about any significant differences between Zelnorm as approved in 2002 and as reintroduced.[65] FDA declines to impose a REMS for Zelnorm.

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[60] Petition at 13.

[61] A copy of this guidance is available at https://www.fda.gov/RegulatoryInformation/Guidances/. When final, this guidance will represent FDA's current thinking on this topic.

[62] Id. at 10.

[63] Indeed, the two drugs approved after FDA issued the 2012 IBS Guidance, linaclotide and plecanatide, did not include identical endpoints and designs in their development programs. Although both measured abdominal pain and stool frequency, the period of response and definitions of responders differed. See FDA-approved labeling for linaclotide and plecanatide at https://labels.fda.gov/. Therefore, prescribers would need to reference the labeling for each product to understand the benefit demonstrated in each respective development program.

[64] Petition at 14.

[65] Id. at 14-15.

The Agency believes that the labeling alone, including a patient Medication Guide, is sufficient to inform an appropriate benefit-risk discussion. Specifically, the potential for CV events is addressed in several sections of the Zelnorm labeling as follows: (1) a contraindication for patients with a history of MI, stroke, TIA, or angina in section 4 (CONTRAINDICATIONS); (2) statements about the CV risks associated with using Zelnorm in section 5 (WARNINGS AND PRECAUTIONS), section 6 (ADVERSE REACTIONS), and section 17 (PATIENT COUNSELING INFORMATION); and (3) a patient Medication Guide to inform patients of the potential risks associated with taking Zelnorm, including CV risks.[66]

Additionally, though the Petition conjectures that providers who prescribed Zelnorm before it was removed from the U.S. Market in March 2007 may not read the current labeling for Zelnorm, FDA believes that prescribers are sufficiently aware of both the safety signal that prompted Zelnorm's removal, including through a Public Health Advisory in 2007, and the October 2018 GIDAC meeting held to discuss reintroducing Zelnorm to the U.S. market.[67] Indeed, members from both the American Gastroenterological Association and the American College of Gastroenterology attended and provided statements at the GIDAC meeting. Given the level of attention to the Zelnorm safety signal and the length of time that has passed since prescribers were able to familiarize themselves with the Zelnorm labeling, we believe that responsible prescribers will consult the new labeling to understand the benefits and risks of the drug before prescribing it to their patients.

As such, the Agency believes that the prominent statements about potential CV risks in the Zelnorm labeling are sufficient to alert prescribers to this concern. Also, as noted above, the CLINICAL STUDIES section of the Zelnorm labeling accurately describes the endpoints and data collected during the Zelnorm clinical trials. The Zelnorm labeling is therefore sufficient to inform an appropriate benefit-risk discussion between prescribers and patients. Additional risk mitigation strategies are not warranted.

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[66] See Multi-Disciplinary Review for Zelnorm at 97. See also, FDA-approved labeling for Zelnorm at https://www.accessdata.fda.gov/scripts/cder/daf/.

[67] See Public Health Advisory: Tegaserod maleate (marketed as Zelnorm), available at https://wayback.archive-it.org/7993/20170113085322/http:/www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051284.htm.

III. CONCLUSION

As discussed above, the Agency today approved sNDA 015 for Zelnorm. FDA is satisfied that the Applicant presented substantial evidence of effectiveness and that the benefits of Zelnorm outweigh its risks when used in accordance with its approved labeling.

Accordingly, the Petition is denied.

Sincerely,

Janet Woodcock
Center Director
Center for Drug Evaluation and Research