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November 21, 2018

BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 02852

CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs refrain from approving any new drug application (NDA) supplement (sNDA) to allow Zelnorm (tegaserod maleate) ("Zelnorm" or "tegaserod") to be marketed 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 the pending sNDA to the Zelnorm NDA (NDA 021200) based on the evidence provided therein, we respectfully request that FDA include post-marketing obligations for the sponsor to conduct new randomized placebo-controlled clinical trials in accordance with the standards identified in current FDA guidance, that 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, and that the sponsor implement a communication REMS[1] to ensure that the benefits of the drug outweigh its risks by making prescribers aware of the important limitations on its use and differences in the new approval compared to the old approval and compared to current standards.

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[1] Risk Evaluation and Mitigation Strategies under section 505-1 of the Federal Food, Drug, and Cosmetic Act ("FDC Act").

I. STATEMENT OF GROUNDS

A. Factual Background

Zelnorm was first approved by FDA in July of 2002 for the short-term treatment of women with irritable bowel syndrome ("IBS") whose primary symptom is constipation ("IBS-C").[2] Zelnorm was subsequently approved in August 2004 for the treatment of "patients less than 65 years of age with chronic idiopathic constipation" ("CIC").[3]

In 2005, FDA identified a potential increased risk of Suicidal Ideation and Behavior ("SI/B") events through the Adverse Event Reporting System. Eventually, in February 2007, FDA recommended that the sponsor of Zelnorm include a description of the potential increased SI/B risk in the product prescribing information. Revised labeling was never implemented[4] because on March 30, 2007, FDA announced that Novartis Pharmaceuticals (the then-sponsor of Zelnorm) had agreed to FDA's request that it voluntarily suspend marketing of Zelnorm in the United States because of a newly identified finding of an increased risk of serious cardiovascular ("CV") adverse events associated with the drug.[5] Based on its assessment of data from 29 placebo-controlled trials, FDA "concluded that the benefit of [Zelnorm] no longer outweigh[s] the risk for the treatment of patients with [IBS-C or CIC]."[6] Zelnorm marketing was discontinued and its marketing status in FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the "Orange Book"), was changed to "Discontinued".[7]

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2 Zelnorm (tegaserod maleate), Approval Letter, NDA 21-200 (Jul. 24, 2002), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/21200ltr.pdf.

3 Zelnorm (tegaserod maleate), Approval Letter, NDA 21-200/S-005 (Aug. 21, 2004), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/21200s005ltr.pdf.

4 FDA Briefing Document Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committees, 1-2 (October 17, 2018) ("FDA Briefing Document") available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM623346.pdf.

5 FDA, Transcript of FDA Press Conference on the Discontinued Marketing of Zelnorm, Dr. John Jenkins, then-Director of the Office of New Drugs speaking, ("2007 Media Call") available at https://wayback.archive-it.org/7993/20170406155414/https:/www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/ucm123719.pdf.

6 2007 Media Call.

7 FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (current through October 2018), https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm.

Since its withdrawal from the market in 2007 and continuing through July 2018, Zelnorm has been made available on a restricted basis under a treatment IND for the treatment of women under the age of 55 with either with either IBS-C or CIC. This treatment-IND has been withdrawn, although Novartis continues to make the drug available on an emergency basis.[8]

In May 2012, FDA issued Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment [9], (the "2012 Guidance") in which FDA sets forth the history and evolution of clinically relevant endpoints in IBS clinical trials and makes recommendations for IBS clinical trial design and appropriate endpoints.

On February 26, 2018, more than ten years after Zelnorm was withdrawn from the market and six years after FDA issued the 2012 Guidance, the new sponsor of the Zelnorm NDA (US WorldMeds, LLC as the authorized U.S. agent for Sloan Pharma, S.a.r.l, "Sloan Pharma") submitted an sNDA proposing to reintroduce Zelnorm to the market with a different and more narrow indication, namely, "the treatment of adult women under 65 years of age with [IBS-C] in a population at low CV risk."[10] This represents a subpopulation of the originally approved patient population (i.e., women with IBS-C who are less than 65 years of age). The sNDA contained no data from new clinical trials.[11]

The sNDA also proposed the following contraindications related to CV safety:

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

In light of these contraindications, the applicant's sNDA can be described as being for treatment of IBS-C in women under 65 with low CV risk. As discussed in more detail below, although the sNDA contains no new clinical data, at FDA's urging, the sNDA includes a *post hoc* efficacy analysis in a subpopulation of IBS-C patients which it characterizes as "severely symptomatic" to support a further limitation on use.[12] FDA encouraged the inclusion of this

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8 FDA, Zelnorm (tegaserod maleate) Information (last updated Jul. 26, 2018), https://www.fda.gov/Drugs/DrugSafety/ucm103223.htm.

9 2012 Guidance, available at https://www.fda.gov/ucm/groups/fdagov-public/documents/document/ucm205269.pdf.

10 FDA Briefing Document at 3. It does not appear that the applicant seeks to reintroduce Zelnorm for the treatment of CIC.

11 *Id.* At 10-11.

12 *Id.* at 2.

analysis should "it be necessary to further restrict the use of tegaserod in this subpopulation to patients with severely symptomatic IBS-C for the benefit to outweigh the potential CV risk."[13]

The sNDA proposed labeling also includes a Warning and Precaution for Major Adverse CV Events (MACE), including cardiovascular death, MI, and stroke: "Evaluate cardiovascular risk factors. Monitor patients and discontinue ZELNORM for development of ischemic cardiovascular disease and discontinue ZELNORM if evidence of cardiovascular disease develops during treatment." In addition, there is a Warning and Precaution for SI/B.[14]

On October 17, 2018, FDA convened a Joint Meeting of the Gastrointestinal Drugs Advisory Committee, and the Drug Safety and Risk Management Advisory Committee (collectively, the "Ad Comm") to review and evaluate questions arising from the sNDA seeking FDA's approval to reintroduce Zelnorm to the U.S. market.

B. Legal Basis

The effectiveness of a new drug must be demonstrated by substantial evidence consisting of adequate and well-controlled investigations that show the drug product will have the effect it purports to have under the conditions of use provided, recommended, or suggested in its proposed labeling. FDC Act § 505 (d); 21 C.F.R. §§ 314.125 and 314.126. Although Zelnorm was previously approved, tegaserod intended for use in the proposed population is a new drug requiring new drug approval prior to marketing.

The sNDA includes a reassessment of the CV risk in light of the proposed subpopulation, but, as described in the Ad Comm materials, it does not include new data to support a finding of safety and effectiveness in the proposed subpopulation of women with reduced CV risk. Nor does it include prospective data to support the more restrictive severely symptomatic subpopulation. Rather, it includes *post hoc* reassessments of >15 year old data in non-randomized subpopulations, which are, by definition, subject to substantial bias. These data are from clinical trials that were not designed in accordance with current standards for IBS studies. Nor has the applicant proposed any bridging analysis to bring reliance on old data into conformity with current standards. As such, the adequacy of the data from the existing clinical trials as measured by the recommended endpoints and statistical analyses can only be guessed at. Consequently, the sNDA for Zelnorm does not contain the requisite substantial evidence for its intended use and should not be approved.

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13 *Id.*

14 *Id* at 3.

1. An approval to reintroduce Zelnorm must be based on a positive risk-benefit assessment for the proposed use in the proposed population.

Any review of tegaserod for reintroduction to the market must include an assessment of the risk-benefit profile for the proposed use in the proposed population. As John Jenkins, M.D., then Director of FDA's Office of New Drugs, stated when announcing Zelnorm's withdrawal from the market in 2007, "[a]ny proposal for reintroduction would require data to identify a patient population where the benefits of Zelnorm might outweigh the risk . . . ."[15] Assessing the risk-benefit profile in a novel population such as that proposed by the applicant requires careful consideration of both the safety and the effectiveness. The effectiveness of a drug must be appropriately assessed in the population for which it is intended to be used.

Although Zelnorm had been approved in 2002 for the short-term treatment of women with IBS-C and in 2004 for the treatment of patients under the age of 65 with CIC, its withdrawal from the market in 2007 due to the CV safety concern triggered a need to reevaluate the risk-benefit profile of the drug in light of the identified safety concern. Moreover, the applicant's proposal for approval for treatment of IBS-C in a distinct subpopulation requires a demonstration of safety and effectiveness of the drug in that subgroup. Although couched in terms of contraindications, the proposed limited indication for use only by women with low CV risk amounts to an indication for a population different from the population for which Zelnorm was originally approved. The same logic applies to the potential more limited indication for treatment of women with IBS-C with low CV risk who are "severely symptomatic."

The effectiveness of Zelnorm has not been evaluated previously in either of these patient subgroups, nor have data from clinical trials designed to evaluate effectiveness in either of these subgroups been included in the sNDA. The fact that the original clinical trials may have included some unknown number of individuals who are members of a newly proposed subpopulation does not equate to a finding of effectiveness in that subgroup.[16] More importantly, to the extent any finding of effectiveness in the original clinical trials is utilized to support approval for a smaller subgroup, the measure of benefit in that subgroup must be established in order to allow for an appropriate risk-benefit evaluation. It cannot be assumed that the same level of response in the broader population studied (modest though that treatment response may have been[17]) can be inferred to have been experienced by the subgroup. In particular, because the number or percentage of women with low CV risk in the original trials

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15 2007 Media Call.

16 We discuss later in this petition the small number of individuals who meet the criteria for severely symptomatic, and the inability to determine what portion of the original population had low CV risk.

17 Three clinical trials supported the original approval. Results from only one of the three trials showed a statistically significant treatment difference between tegaserod and placebo. FDA Briefing Document at 11-13.

cannot be ascertained from the available information about participants in those trials conducted more than 15 years ago, it is not known whether the data are sufficient to support a determination that the overall treatment effect demonstrated in the full population applies equally to the smaller subgroup. In fact, it is quite possible that the low risk CV group (if it could be identified and subjected to a *post hoc* analysis) experienced a different treatment effect than the overall population experienced.

The potential for such a generalization of efficacy to be misplaced increases as the number of women with low CV risk in the >15 year old studies that led to the 2002 approval of Zelnorm decreases. Unfortunately, we do not know the CV risk profile of these study subjects as the enrollment criteria for the studies did not require the exclusion of individuals who would not meet the definition of "low risk" being proposed by the applicant. As described in the Ad Comm materials, the proposed limitation on use of Zelnorm to women at low CV risk excludes not only those with a history of CV ischemic disease (such as MI, stroke, transient ischemic attack or angina), but also those with more than one CV risk factor: hypertension, tobacco use, diabetes, hypocholesterolemia, age ≥55 years, or obesity. It is unknown how many study subjects in the > 15 year old original Zelnorm trials had these risk factors.

Although the focus of the Ad Comm meeting was on the reevaluation of CV risk in potential subgroups (IBS-C females, IBS-C females with low CV risk, IBS-C females who are "severely symptomatic," and IBS-C females at low CV risk and who are "severely symptomatic"), any such reevaluation must be done in light of the benefit demonstrated for the same subgroup population.

In the Ad Comm materials, FDA stated that the focus of the review team's reanalysis of the original data was to determine whether the efficacy demonstrated in the original patient population that supported approval was "comparable" in a subpopulation of severely symptomatic females with IBS-C.[18] Notable is the absence of any reanalysis of the efficacy data in the subgroup of women with low CV risk.[19] Thus, FDA's recent review of the efficacy data for the proposed population of women with low CV risk considered data from all women in the three original pivotal trials (B301, B358 and B307) and in a fourth trial (Study B351) without regard to CV risk – a different patient population than the one that could be exposed to the drug if the sNDA is approved.

Similarly, when evaluating efficacy data for the more limited proposed subgroup of severely symptomatic women with low CV risk, FDA reviewed data for what it defined as severely symptomatic women from the studies done in support of the original approval without regard to CV risk. FDA stated without explanation that during the review of the sNDA, the FDA

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18 *Id.* At 10.

19 We put aside for the moment whether a study that does not meet current standards based on more up-to-date understanding of IBS should be the basis of an approval.

team decided that "CV risk should not influence the efficacy of the drug," and asked the sponsor to remove "no history of major adverse cardiac events" from the criteria for defining severely symptomatic.[20]

In assessing the efficacy of Zelnorm in women with low CV risk, the sNDA relies on the three original pivotal trials that did not exclude patients who were obese, smoked, or suffered from hypertension, diabetes, hypocholesterolemia.[21] Perhaps most significantly, of these three pivotal trials, only one, B301, showed a statistically significant treatment difference in the overall population studied. The other two trials showed smaller differences that were not statistically significant.[22] Data from a fourth trial (B351) which was considered exploratory at the time and not used to support the original approvals, was also included to support the sNDA.[23] The modest size of the treatment effect (the difference between tegaserod and placebo) should not be ignored. In Trials B307 and B358, the treatment effect was 5.3% and 4.7%, respectively (neither of which was statistically significant), and the treatment effect was 11.4% in B301.[24] The treatment effect was slightly bigger (14.2%) in B351.[25] FDA reviewers also expressed concerns about, among other things, the potential confounding use of laxatives in the original studies making it difficult to interpret reported results of relief.[26]

Thus, the evidence of efficacy on which the sNDA relies for approval of an indication for women with low CV risk is limited to results from clinical trials that were not designed to evaluate this potential patient group, and in which two of three studies did not show a statistically significant effect, while the fourth study was exploratory. The potential for such studies to overstate any benefit to a particular subgroup cannot be characterized without an

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20 FDA Briefing Document at 13.

21 As discussed in more detail below, this endpoint does not reflect the current medical standards for clinical trials for IBS-C.

22 FDA Briefing Document at 12-13.

23 *Id.* at 10-11. The applicant also submitted trial data from two postmarketing requirements (A2306 and A2417) which FDA determined were not appropriate for inclusion in the analysis of the proposed subpopulation.

24 FDA Briefing Document at 13, Table 2.

25 As noted in one of the medical officer reviews for the original NDA, "tegaserod demonstrates efficacy which [is] modest using the primary parameter of efficacy." FDA, Division of Gastrointestinal and Coagulation Drug Products, Medical Officer's Review, NDA 21-200, 32 (Dec. 15, 2000), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm_medr_P1.pdf.

26 FDA, Memorandum, NDA 21-200 – ZELMAC™ (tegaserod; HTF 919): Recommendations for Regulatory Action, from Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, Division of Gastrointestinal and Coagulation Drug Products (July 17, 2000), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm_admindocs_P1.pdf.

analysis of that subgroup unless the subgroup makes up a significant majority of the overall group – a fact that does not appear to be the case. The studies that the applicant proposes to rely on cannot be used to define the benefit for purposes of establishing the risk-benefit profile of tegaserod for women with low CV risk or for severely symptomatic women with low CV risk.

2. A post hoc analysis of a subgroup identified only after completion of the clinical trials that supported the original approval is not adequate support for approval of the new indication.

In its Ad Comm briefing package, FDA outlined many of the shortcomings of the data providing evidence of tegaserod effectiveness in the new subpopulation. Significantly, in discussing the efficacy review in the severely symptomatic subgroup, FDA stated that "[t]he efficacy review strategy is based on *post hoc* analyses of completed trials."[27] The concept of revisiting data from a failed clinical trial in an attempt to salvage some subgroup for which positive data can be pieced together when the subgroup was not identified prior to study initiation is a practice FDA consistently discourages in most scenarios, rightly pointing out the potential for bias. "Although *post hoc* analyses of trials . . . 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. . . . Consequently, *post hoc* analyses by themselves cannot establish effectiveness."[28] The analyses conducted for the sNDA are a textbook example of how a subgroup can be identified for additional future testing in a randomized controlled clinical trial designed to study effectiveness in that subgroup. Approving a drug on such a basis is, however, inconsistent with existing FDA policy.

The potential bias introduced by the *post hoc* approach is even more profound in the application of the definition of "severely symptomatic." Severely symptomatic was defined as female patients with IBS-C reporting:

- 3 or more days per week with severe or very severe abdominal pain and discomfort; and,
- 5 or more days per week with hard, very hard, or no stools.[29]

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27 FDA Briefing Document at 10.

28 FDA, Draft Guidance for Industry, Multiple Endpoints in Clinical Trials, Draft Guidance, 8 (January 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf.

29 FDA Briefing Document at 14. FDA also notes that there was no agreement between the applicant and FDA on the definition prior to submission of the sNDA.

FDA pointed out that in selecting the individuals to include in the subgroup analysis, the applicant applied the most permissive of three possible approaches to rounding to determine stool frequency (one of the subgroup criteria), thereby increasing the number of patients included in the subpopulation. For example, under the most permissive approach, for an individual reporting 2.1 days per week with severe abdominal pain, the number would be rounded up to 3 days and that individual would be included as severely symptomatic. Under a "no rounding" approach, or an approach of rounding up at 0.5 and down if below 0.5, the same individual would be considered to have 2 days per week and, therefore, would not be considered severely symptomatic and would be excluded from the analysis. Regardless of the rounding option used, the subgroup population is significantly smaller than the original population studied, further diminishing the value of the *post hoc* subgroup analysis. For example, in Study 301, the original sample size was 484. Using the most permissive rounding option chosen by the applicant, the sample size for severely symptomatic females is reduced to 135 (28%) while using the no rounding method results in a sample size of 74 (15%). Similar reductions in sample size are observed when the different rounding options are applied to studies 307 and 351, and to a somewhat lesser extent in study 358.[30]

Moreover, in addition to affecting the number of patients included in the subpopulation analysis, when FDA compared the results using the three rounding methods, it found that the treatment effects were notably different across trials, and that there were no consistent trends depending on the rounding methods (in three trials, the treatment difference generally decreased as the degree of severity increased, but in another, the treatment difference increased as severity increased).[31]

FDA described a further limitation on the utility of data that is more than 15 years old to support the current application. With respect to the requirement that the individual have fewer than three complete spontaneous bowel movements ("CSBMs") per week, FDA stated that because the original trial data did not include specific timing information on the use of laxatives or ask whether a bowel movement ("BM") was complete, it is not feasible to determine whether a BM was spontaneous or complete, and therefore, 40-75% of the patients included in the severely symptomatic population would be excluded based on the current guidance.[32] This additional drawback highlights significant limitations associated with using data that is more than 15 years old and collected under different and less rigorous standards to measure a treatment effect – a critical component of the risk-benefit assessment needed to support approval.

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30 *Id.* at 14.

31 *Id.* at 20-21, 24-25.

32 *Id.* at 18-19.

3. Zelnorm's effectiveness has not been evaluated under current standards.

The sNDA for Zelnorm does not contain the requisite substantial evidence for its intended use. It fails to include new data to support a finding of safety and effectiveness in the proposed subpopulation of women with reduced CV risk, and similarly fails to include data to support the more restrictive severely symptomatic subpopulation. Rather, it includes *post hoc* reassessments of greater than 15 year old data in non-randomized subpopulations that are, by definition, subject to substantial bias. Accordingly, the sNDA should not be approved.

The risk-benefit calculation required for approval today must take into consideration the level of benefit as benefit to IBS-C sufferers is currently understood. Further, the evaluation of the effectiveness of Zelnorm in a new subpopulation should be conducted using the current scientific and medical understanding of IBS. The three clinical trials that supported the original approval of Zelnorm utilized a single general item asking patients to rate change in their overall IBS-C symptoms as a primary endpoint to support an efficacy claim.[33] As FDA notes in the 2012 Guidance, "a single general item cannot adequately capture whether benefit is achieved in all, or only some, of the important signs and symptoms. For example, a single item that queries a patient about his or her overall IBS experience will likely not capture a situation where the patient's stool frequency has improved, but abdominal pain has not improved or even worsened."[34] The trial design supporting the original approval of Zelnorm does not meet current standards as set forth in the 2012 Guidance.

The medical and scientific understanding of what is clinically meaningful to sufferers of IBS-C has grown in the more than 15 years since the original approval of Zelnorm. The Rome Foundation, recognized as the international authority for categorizing gastrointestinal functional disorders and their pathophysiology, has twice updated their diagnostic guidelines for IBS during this time. The current criteria (Rome IV)[35] include significant changes from Rome II (issued during Zelnorm's legacy trials), including removal of abdominal discomfort as a primary symptom – instead focusing on abdominal pain. FDA's guidance and recommendations on appropriate endpoints have similarly evolved, and today, to be deemed an "overall responder" to drug treatment, the patient must achieve "the prespecified improvement in weekly or daily response for at least 50 percent of the weeks or days of treatment (e.g., 6/12 weeks or 42/84 days)."[36] For IBS-C specifically, the 2012 Guidance provides that a "patient is categorized as a weekly responder if the patient is a weekly responder in **both**

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33 FDA Briefing Document at 10.

34 2012 Guidance at 3-4.

35 FDA Briefing Document at 4.

36 *Id.* at 7. Moreover, for a drug approved in 2017 for IBS-C (plecanatide), FDA required that the endpoint be met in 3 of the final 4 weeks of treatment. *See*, CDER, NDA 208745, Division Director Summary Review

[abdominal] pain intensity **and** stool frequency."[37] FDA defines an "Abdominal Pain Intensity Weekly Responder" as a "patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score (measured daily) of at least 30 percent compared with baseline weekly average," and defines a "Stool Frequency Weekly Responder" as a "patient who experiences an increase of at least one CSBM per week from baseline."[38]

Clearly, the endpoints used in the clinical trials that supported the 2002 and 2004 approvals of Zelnorm fail to meet the standards set forth in the 2012 Guidance and, thus, would not support approval today. Nevertheless, the sNDA relies on the original clinical trials and post-marketing studies that were not designed in a manner that would support the proposed indication under the current FDA standards. As FDA noted in the Ad Comm materials, the Agency's "approach to the evaluation of efficacy in clinical trials of products for the treatment of IBS-C has evolved since the original tegaserod approval; however, no new trials were conducted to support reintroduction to the market."[39] Significantly, in its Ad Comm materials, FDA stated that because of the design differences, "it is difficult to compare the original IBS-C trials with the current FDA recommended approach."[40]

Specifically, in contrast to studies conducted under the 2012 Guidance – which calls for study subjects to record daily abdominal pain intensity and stool frequency (as measured by CSBMs),[41] the primary endpoint for the Zelnorm clinical trials which were conducted more than 10 years before FDA issued the 2012 Guidance, was measured using a single question asking subjects to compare how they "felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit."[42] FDA specifically stated in the 2012 Guidance that such patient ratings of change as a primary endpoint are not recommended because a single general item cannot adequately capture the treatment effect on all of the clinically important signs and symptoms of IBS, but recommended such ratings as "exploratory endpoints."[43]

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for Regulatory Action from Donna Griebel, MD, 8 (Jan. 19, 2017) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208745Orig1s000SumR.pdf.

37 2012 Guidance at 8.

38 *Id.*

39 FDA Briefing Document at 10-11.

40 *Id.* at 18.

41 2012 Guidance at 7-10.

42 FDA Briefing Document at 11.

43 2012 Guidance at 9.

The reevaluation of both safety data and effectiveness data to support reintroduction must be conducted under current scientific and medical standards as set forth in the 2012 Guidance. We recognize that FDA guidance is not binding and that sponsors may choose an alternative approach to demonstrate safety and effectiveness. We note, however, that the last two drugs approved for IBS-C, Linzess (linaclotide, NDA 202811)[44] and Trulance (plecanatide, NDA 208745) [45] adhered to the 2012 Guidance. Further, the applicant does not appear to be proposing an alternative to the 2012 Guidance, it is proposing to ignore it. In this case, however, FDA has specifically identified the shortcomings of single endpoint studies such as those supporting the original Zelnorm approval and specifically noted the confusion that results from the terminology used in the original Zelnorm studies (discomfort), as an example of an inadequately informative endpoint. In fact, in describing the shortcomings of endpoints previously used for IBS drug approvals, the 2012 Guidance specifically identifies tegaserod and the single yes-no question used to assess efficacy, noting that although the endpoints used for tegaserod "may well have captured the direction of change (trials were controlled and blinded), they could not provide useful information on the effect of treatment on the severity of a specific sign or symptom."[46]

FDA also noted in the 2012 Guidance that although previous IBS clinical trials assessed abdominal "pain or discomfort," it is not clear whether the abdominal pain and the abdominal discomfort experienced by patients with IBS are synonymous or two different symptoms. FDA stated further that although adequate qualitative trials have not fully addressed these questions, clinical data provided to and reviewed by FDA suggest that abdominal pain and discomfort may be different symptoms that should be assessed by different questions and that the chronic pain literature suggests that pain intensity may be a more clinically relevant assessment than pain frequency. The endpoint used in the three primary original clinical trials does not distinguish between pain and discomfort, and instead assesses them as a single endpoint using questions that fail to distinguish between the two.

In order to make an informed decision about which drug to prescribe to a specific patient, a prescriber of IBS drugs needs to understand the specific benefits and risks of the drugs that are available. Prescribers are likely to understand that a 2018 approval of Zelnorm means that the drug was found to be safe and effective under 2018 standards as described in the applicable 2012 Guidance. More specifically, prescribers are likely to believe that this drug approved in 2018 would be effective at reducing pain and increasing stool frequency.

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[44] CDER, NDA 202-811, Division Director Review from Donna Griebel, MD (Aug. 29, 2012), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000SumR.pdf.

[45] CDER, NDA 208-745, Division Director Summary Review for Regulatory Action from Donna Griebel, M.D. (Jan. 19, 2017), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208745Orig1s000SumR.pdf.

[46] 2012 Guidance at 2-3.

FDA specifically recognized the shortcomings of the tegaserod studies six years ago in the 2012 Guidance. It defies logic that the same data should be sufficient to support a new carved-out IBS-C indication today.

4. If Zelnorm is approved, its labeling must reflect the limitations of the data on which the approval is based.

In accordance with 21 U.S.C. § 352(f), a drug is misbranded "[u]nless its labeling bears . . . adequate directions for use . . . ." FDA regulations at 21 C.F.R. § 201.100(c)(1) provide that a drug may satisfy the statutory requirement that its labeling bear adequate directions for use, if its "[l]abeling . . . bears adequate information for its use, including . . . any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented . . . ." If approved[47], the content of the prescribing information for Zelnorm will not meet this regulatory standard because it will not provide adequate directions for use in the proposed patient population. This is because the prescribing information will not reflect the limitations – that the clinical trial results pertain to a different population and that the "treatment effect" set forth in the prescribing information is derived from studies that do not align with the current standards that have been in place since they appeared in the 2012 Guidance. In fact, the actual relevant treatment effect is unknown due to the lack of information about what is considered clinically relevant and important now. As described in the 2012 Guidance, the data provided by the greater than 15 year old trials are not capable of measuring the clinical benefit to IBS-C sufferers. In order for the prescribing information for Zelnorm to provide prescribers with adequate accurate information for determining whether the drug is appropriate for a given patient, the prescribing information must include explanations of the limitations of the evidence on which its approval is based, particularly where, as is the case for Zelnorm, the evidence is not what would be expected to support an IBS-C application approved in 2018. Such limitations of use should be properly noted in the *Indications and Usage* section of the approved labeling. 21 C.F.R. § 201.57 (a)(6).

If the Zelnorm sNDA is approved for use by patients who are severely symptomatic, it is also important that the significance of "severely symptomatic" is properly understood by prescribers as a limitation on use to those who experience severe symptoms and do not experience relief from other available treatments. Without a limitation to use by those individuals who are both severely symptomatic and who also are refractory to other treatments, the indication could be misunderstood as meaning that Zelnorm should be used as a first-line of treatment in more severe cases because it works better than other currently available FDA-approved therapies, rather than because it is less safe and should be reserved for use when other treatments fail.[48]

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[47] We note that our discussion of possible labeling issues or post-marketing requirements should not be interpreted as agreement that the Zelnorm sNDA can be approved based on the current data.

[48] An example of the use of such a limitation in a drug reintroduced for use only in severely symptomatic

The Clinical Studies section of the current Zelnorm approved labeling should also be revised to reflect present-day standards, so as not to highlight results that are no longer recognized as sufficiently evidence-based or that were obtained using obsolete assessment methods. In particular, the Clinical Studies section of the current Zelnorm labeling describes results from a variety of individual symptoms including bloating. In the time since the original Zelnorm approval, the methods of assessment and nature of evidence required for a bloating labeling claim have become more rigorous. Highlighting existing results related to bloating by inclusion in the Zelnorm label would imply the quality and level of evidence used to assess bloating were up to current standards. The description of Clinical Studies in 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 upon evidence collected employing current methods of assessment.

5. If the Zelnorm sNDA is approved without additional data, the approval should include a post-marketing requirement to demonstrate the effectiveness of Zelnorm in the approved population under current standards.

If FDA approves the Zelnorm sNDA despite the shortcomings of the supporting evidence, the approval should be accompanied by a post-marketing requirement ("PMR") that the sponsor conduct and complete within 24 months of approval an appropriate confirmatory study under the 2012 Guidance to determine whether the drug is safe and effective as a second line of treatment for the proposed patient population under current standards.

6. If the Zelnorm sNDA is approved, the sponsor should be required to implement an approved REMS.

If the Zelnorm sNDA is approved and the drug is reintroduced to the market, it is imperative that the differences between the 2002 conditions of approval and the 2018 conditions of approval are communicated to all prescribers. Specifically, prescribers who will include not only specialists, but also primary care physicians, must be made aware that the drug is being reintroduced for a narrower indication. Both groups of prescribers are likely to assume that the indication and limitations on use of the Zelnorm that returns to market are the same as the indications and limitations on use of the Zelnorm that was withdrawn from the market in 2007. In fact, prescribers are likely to mistakenly believe that the CV risk identified in 2007 has been "resolved," and is no longer considered an impediment to safe and effective use. Even if the prescribing information contains the limitations on use described in this petition, an inherent and unique risk exists that prescribers who were familiar with Zelnorm ten years ago will assume they are familiar with this "old" drug and may start prescribing it without revisiting the

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cases is in the prescribing information for Lotronex which includes an indication for severe IBS-D who have not responded to adequately to conventional therapy. See, Lotronex (alosetron hydrochloride) Tablets Prescribing Information, NDA 021107 (Jan. 2016) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021107s027lbl.pdf.

prescribing information in detail. As noted in the official minutes of the Ad Comm meeting, "Members also expressed the importance of a risk-benefit discussion between patient and provider prior to use of Zelnorm."[49]

In order to ensure that the benefits of this drug outweigh its risks and that the significant differences between Zelnorm as approved in 2002 and reintroduced in 2018 are understood by prescribers and discussed with patients, an appropriate REMS should be required under FDC Act section 505-1. Such a REMS could take a number of forms, but at a minimum should include a communication plan to inform healthcare providers.

7. Lack of an approved drug with the same mechanism of action does not negate the requirement for a positive risk-benefit profile for approval.

The availability of other proven and approved treatments for the same condition enters into the risk-benefit calculation when determining the approvability of a drug. In general, a higher level of risk may be acceptable when no other treatment options exist for that disease state, as is a lower level of benefit either in terms of the percent of individuals likely to receive a benefit or in the clinical significance of the benefit. In 2018, more drugs are available for treating IBS-C than were available when Zelnorm was first approved in 2002. Consequently, it is even more important that the sNDA demonstrates a positive risk-benefit profile than was the case when it was originally approved.

Zelnorm is a 5-HT_4 receptor agonist with high affinity at human 5-HT_4 receptors and with moderate affinity for 5-HT_1 receptors. Although no other approved products indicated for IBS-C utilize the same mechanism of action, this factor does not negate the need for substantial evidence of effectiveness, particularly when other drugs are available and have demonstrated safety and efficacy in the treatment of IBS-C.

We understand that there are some individuals for whom the Zelnorm mechanism of action may provide unique relief. Based on the small number of individuals testifying at the Ad Comm, the size of that patient group appears to be relatively modest. If the Zelnorm sNDA is not approved, Zelnorm can continue being made available as it has been since 2007 when it was removed from the market until such time, if ever, that its safety and effectiveness are demonstrated under current standards. In addition to other exclusion criteria related to CV risk, eligibility requirements for a single patient IND include that there be no comparable or satisfactory alternative drug or therapy available to the patient.[50]

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[49] FDA, Summary Minutes of the Gastrointestinal Drugs Advisory Committee (October 17, 2018) 6, available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM626241.pdf.

[50] FDA, Zelnorm Single Patient IND Packet (last updated June 2018), available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM490129.pdf.

Moreover, if it appears that a distinct group of IBS-C sufferers might benefit from mechanism of action of Zelnorm, then it would be appropriate to conduct a new clinical study to better define that group, when the drug should be used (e.g., as second-line treatment), and the clinical benefit provided.

8. The Advisory Committee discussion and questions focused on whether the CV safety risk had been adequately evaluated and its voting reflects that focus.

Of the five questions posed to the Ad Comm, three were specific to the safety profile – the strength of the CV safety signal, other safety concerns including SI/B, and a general question about available safety data. A fourth question asked whether the therapeutic gain is "generally similar in magnitude" between the severely symptomatic population and the originally approved population, and the fifth and final question asked whether the benefits would be expected to outweigh risks in specified subgroups.[51] The discussion of CV safety dominated the Ad Comm's discussion with far less discussion of effectiveness. This is not surprising given the statement in FDA's Briefing Document that "FDA is not asking the Advisory Committee to reanalyze the efficacy of tegaserod for the treatment of IBS-C for which tegaserod is approved."[52]

II. ACTIONS REQUESTED

We respectfully request that FDA refrain from approving the pending or any other sNDA to reintroduce Zelnorm to the market unless:

(1) the application provides substantial evidence of safety and effectiveness in the population or subpopulation proposed for the intended use that meets current standards; or, in the alternative,
(2) if FDA approves an application that allows the marketing of Zelnorm without such substantial evidence, the conditions of approval include:

- a PMR for the sponsor to conduct and complete a randomized, well-controlled clinical trial to demonstrate the safety and effectiveness of Zelnorm in the approved population under current standards within a specified time period no longer than 24 months after approval;
- approved labeling that specifically reflects the lack of substantial evidence of effectiveness under current standards and reliance on *post hoc* analysis of data

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51 FDA, Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting Questions (Oct. 17, 2018), available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM624087.pdf.

52 FDA Briefing Document at 2.

not designed to demonstrate evidence of effectiveness in the relevant population; and,

- a communication REMS to ensure that prescribers are aware that reintroduction of Zelnorm to the market is for a more limited population than that for which it was originally approved and that concerns with CV safety remain.

III. ENVIRONMENTAL IMPACT

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. § 25.31(a).

IV. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

V. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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DLL/tee

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