ZELNORM™

(tegaserod maleate)

For the treatment of Irritable Bowel Syndrome with Constipation (IBS-C)

ERRATA TO THE BRIEFING DOCUMENT

FDA Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee

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APPLICANT: Sloan Pharma, US WorldMeds

ADVISORY COMMITTEE BRIEFING MATERIALS

AVAILABLE FOR PUBLIC RELEASE.

1. INTRODUCTION

The following errors have been identified in the Sponsor's briefing document prepared for GIDAC and DSaRM advisory committees. These identified errors do not carry through to other sections of the briefing materials and do not affect the overall conclusions as stated in the briefing document. The errors are identified by a ~~strikethrough~~ with corrections identified in **bold** text below.

2. IDENTIFIED ERROR

2.1. Error 1: Pages 15 and 17 Section 3.1 Adjudication History

In footnotes of Table 2 (page 15) and Table 4 (page 17), proportion differences and 95% CIs were presented. The Sponsor seeks to clarify the p-values presented were from Fisher's exact tests. Additionally, typographical error in the 95% CI ~~(-0.00, 0.012~~) in footnote c of Table 2 was noted. The correct 95% CI should be (**-0.003, 0.12**).

2.2. Error 2: Page 17 Section 3.1 Adjudication History

It is stated that 'two of the patients with MACE events had a history of CV ischemic disease in addition to CV risk factors'. According to patient narratives in the adjudication report, one additional subject was identified as having a previous history of CV disease. As such, the text on page 17 should reflect that **three out of four MACE subjects** had a prior history of CV disease at baseline.

2.3. Error 3 Page 23 Section 3.3.4 Platelet Aggregation

In the prior Sponsor study RD-2008-00298 (Serebruany, 2010), pre-incubation with tegaserod at concentrations mimicking human C_{max} values (10 nM), 3.3-times C_{max} (33 nM) and 10-times C_{max} (100 nM), respectively, resulted in minor increases in platelet aggregation induced by ADP, collagen, epinephrine, or 5-HT. exposures (>3.3X clinical C_{max} plasma levels for humans)By contrast,~~ two~~ **three** other in vitro studies were conducted by independent investigators (Higgins, 2012; Beattie, 2013; Conlon, 2018)~~,~~**.** In these studies investigators used methods that produce a more stable platelet preparation.

2.4. Error 4: Page 35 Section 5.2 Clinical Efficacy Overview

The Sponsor states that the approval of tegaserod "was based on 3 placebo-controlled, 12-week clinical trials (B301, ~~B351~~ and B358, see Section 5.2.1), with data from a dose titration study included (B307)." This statement should be updated to state that **the three original trials supporting approval and described in the label were trials B301, B358, and B307**.[1] **Trial B351 was considered exploratory at the time of the original approval**.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21200lbl.pdf

2.5. Error 5: Page 38 Section 5.2.1.1. Primary Efficacy Endpoint and Results; Figure 9

In Figure 9: "Between-treatment Comparisons of the Percent of Patients Responding to SGA of Relief (Primary Efficacy) During 50% of Month 1 and the Last 4 Weeks of Treatment (Endpoint) in Studies B301, B351, and B358-Females Only" the therapeutic gain for study 358 at endpoint should be **4.7%** not ~~5.3%~~. The 5.3% value reported was a result from analyses where baseline laxative use was adjusted for. To remain consistent with the pre-specified analyses, the therapeutic gain has been updated to reflect analyses not adjusting for baseline laxative use.

2.6. Error 6: Pages 44 and 46 Section 5.2.2 Exploratory Analyses for Reintroduction; Figures 14 and 15

Given the type of data collected during the completed trials and exploratory nature of applying the data to the 2012 IBS Guidance recommendations, it is important to refer to this endpoint as a variation of the 2012 IBS Guidance Endpoint. Therefore, the titles of Figures 14 and 15 and related contents in Section 5.2.2 of the briefing document you should specify that this endpoint is a "**Variation of the 2012 IBS Guidance Endpoint**." The endpoint was based on original secondary endpoints, not on the currently recommended endpoints in the Guidance.

2.7. Error 7: Page 46 Section 5.2.2 Exploratory Analyses for Reintroduction; Figure 15

A typographical error was made in the therapeutic gains presented in Figure 15, entitled "Therapeutic Gain in Females with Severe IBS-C Assessed Using the 2012 IBS Guidance Co-Primary Endpoint". The therapeutic gain should be changed for study 301 from ~~12.7%~~ to **15.2%.**

2.8. Error 8: Page 49 Section 5.2.3.3 Figure 17

The values presented in Figure 17 in the Sponsor's briefing document were determined to be incorrect based on the incorrect number of patients represented in the IBS-C group of study 2417. N= ~~337~~ **336**

2.9. Error 9: Page 51 Section 6.1 Databases Used for Safety Analyses; Table 11

The values presented in Table 11 in the Sponsor's briefing document were determined to be incorrect based on the incorrect number of patients represented in the IBS-C group of study 2417. Table 11 is duplicated below (in Table 1) with updates to reflect accurate numbers for the IBS-C studies and clarify the non-IBS-D indication by separating out the IBS-M population.

Table 1: Indications and Number of Patients Contributing to Safety Database 15

Indication	Number of Studies	Number of Patients N (% contributing to overall database)
IBS-C	10	~~7,948 (42.6)~~ **8,284 (44.4)**
CIC	4	3,531 (18.9)
Functional dyspepsia	6	3,522 (18.9)
IBS-D	2	162 (0.9)
~~IBS-M (IBS-C +~~ **non IBS-D**~~)~~	~~3~~ **2**	~~1,823 (9.7)~~ **1,163 (6.24%)**
IBS-M	**1**	**324 (1.74%)**
Slow transit constipation (STC)	1	12 (0.1)
GERD	2	1,526 (8.2)
Diabetic gastropathy	1	121 (0.6)

2.10. Error 10: Page 73 Appendix 3; Table 17

To improve the clarity of meaning for the values in the following column in Table 17 "Human Cmax Relative Binding Threshold (10 nM)", the values in this column were calculated by dividing the Ki (nM) by the human Cmax (10 nM).

2.11. Error 11: Page 77 Appendix 6

(b) (6) also has a **history of CV disease**

(b) (6) also has a **history of smoking**

2.12. Error 12: Page 90 Appendix 9 Epidemiological Data

An error was noted in the statement "Suicide attempt and self-inflicted poisoning/injury was reported in 25 (0.048%) tegaserod users and in 32 (0.065%) in non-users, and suicide attempt and self-inflicted poisoning/injury with outcome death in one (0.002%) tegaserod users and in no non-user." This statement should have the following correction to ~~32 (0.065%)~~ **34 (0.067%) non-users** with suicide attempt or self-inflicted poisoning/injury.

2.13. Error 13: Page 91 Appendix 9; Overall Conclusions

Preclinical data do not suggest that tegaserod at therapeutically relevant doses has a potential for CNS effects. Single dose experiments showed ~~a mild moderate blood brain~~ **minimal blood-brain** penetration of tegaserod in animal models, however, its predictability for humans is unknown.