Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Gastrointestinal Drugs Advisory Committee
October 17, 2018

Location: Bethesda Marriott, the Grand Ballroom, 5151 Pooks Hill Road, Bethesda, Maryland

Topic: The committee discussed supplemental new drug application (sNDA) 021200, supplement 015, for ZELNORM (tegaserod maleate) tablets for oral administration, submitted by Sloan Pharma S.à.r.l, Bertrange, Cham Branch, proposed for the treatment of women with irritable bowel syndrome with constipation who do not have a history of cardiovascular ischemic disease, such as myocardial infarction, stroke, transient ischemic attack, or angina, and who do not have more than one risk factor for cardiovascular disease.

These summary minutes for the October 17, 2018 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on November 7, 2018.

I certify that I attended the October 17, 2018, meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jay R. Fajiculay, PharmD
Designated Federal Officer, GIDAC

/s/
Jean-Pierre Raufman, MD
Chairperson, GIDAC

Summary Minutes of the
Gastrointestinal Drugs Advisory Committee Meeting
October 17, 2018

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 17, 2018 at the Bethesda Marriott, the Grand Ballroom, 5151 Pooks Hill Road, Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from the FDA and Sloan Pharma/US WorldMed. The meeting was called to order by Jean-Pierre Raufman, MD (Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD (Designated Federal Officer). There were approximately 110 people in attendance. There were three Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed supplemental new drug application (sNDA) 021200, supplement 015, for ZELNORM (tegaserod maleate) tablets for oral administration, submitted by Sloan Pharma S.à.r.l, Bertrange, Cham Branch, proposed for the treatment of women with irritable bowel syndrome with constipation who do not have a history of cardiovascular ischemic disease, such as myocardial infarction, stroke, transient ischemic attack, or angina, and who do not have more than one risk factor for cardiovascular disease.

Attendance:
Gastrointestinal Drugs Advisory Committee Members Present (Voting): Joy McVey Hugick, BA (Consumer Representative); Sandeep Khurana, MBBS; Benjamin Lebwohl, MD, MS; Jean-Pierre Raufman, MD (Chairperson); Rachel L. Rosen, MD, MPH

Gastrointestinal Drugs Advisory Committee Members Not Present (Voting): David N. Assis, MD; Lin Chang, MD; Christopher S. Coffey, PhD, MS; Jennifer C. Lai, MD, MBA; Darrell S. Pardi, MD, MSc; Lisa L. Strate, MD, MPH

Gastrointestinal Drugs Advisory Committee Member Present (Non-Voting): Douglas Levine, MD (Industry Representative)

Temporary Members (Voting): Sally Hunsberger, PhD; J. John Mann, MD; Sabrina Numann (Patient Representative); Suzanne B. Robotti (Acting Consumer Representative); Steven F. Solga, MD; John Teerlink, MD; Udho Thadani, MD

FDA Participants (**Non-Voting):** Julie Beitz, MD; Joyce Korvick, MD, MPH; Preeti Venkataraman, MD; Sandhya Apparaju, PhD; Joel Weissfeld, MD, MPH

Designated Federal Officer (Non-Voting): Jay R. Fajiculay, PharmD

Open Public Hearing Speakers: Neal Osborn, MD, MSc (American College of Gastroenterology), Peter Kaufman, MD (American Gastroenterological Association), Jeffrey Roberts, MSEd, BSc (IBS Patient Group)

The Agenda was as follows:

Call to Order and Introduction of Committee	**Jean-Pierre Raufman, MD** Chairperson, GIDAC
Conflict of Interest Statement	**Jay Fajiculay, PharmD** Designated Federal Officer, GIDAC
FDA Introductory Remarks	**Preeti Venkataraman, MD** Clinical Team Leader Division of Gastroenterology and Inborn Errors Products (DGIEP) Office of Drug Evaluation (ODE) III Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Sloan Pharma S.a.r.l., Bertrange, Cham Branch**
Zelnorm™ History and Program Introduction	**Kristen Gullo** VP, Development & Regulatory Affairs US WorldMeds
Cardiovascular Safety Evaluation	**Philip Sager, MD, FACC, FAHA** Adjunct Professor of Medicine Stanford University of Medicine
General Safety and Efficacy Overview	**Rachael Gerlach, PhD** Regulatory Science Manager US WorldMeds
Medical Landscape and Benefit-Risk	**Colin Howden, MD** Chief, Division of Gastroenterology University of Tennessee Health Science Center
Sponsor Commitments	**Kristen Gullo**
Clarifying Questions to the Presenters	
BREAK	
FDA PRESENTATIONS	
Clinical Efficacy in Severely Symptomatic IBS-C Female Patients	**Irena Lavine, MD** Medical Officer DGIEP, ODE III, OND, CDER, FDA

Nonclinical Safety Findings of Tegaserod	**Ke Zhang, PhD** Pharmacology Reviewer DGIEP, ODE III, OND, CDER, FDA
Clinical Pharmacology Findings of Tegaserod	**Jie Cheng, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology III Office of Clinical Pharmacology Office of Translational Sciences (OTS) CDER, FDA
Clinical Safety Evaluation	**Sandhya Apparaju, PhD** Safety Reviewer DGIEP, ODE III, OND, CDER, FDA
Cardiovascular Outcomes Meta-Analysis of Clinical Trials	**Thanh Tran, PhD** Safety Statistical Reviewer Division of Biometrics VII Office of Biostatistics, OTS, CDER, FDA
An Assessment of a Cohort Study of Tegaserod and Cardiovascular Events	**Joel Weissfeld, MD** Medical Officer Division of Epidemiology I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology CDER, FDA

Clarifying Questions to the Presenters

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/ Committee Discussion

BREAK

Questions to the Committee/ Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the strength of the potential CV safety signal of tegaserod, considering the totality of available data from clinical trials, adjudications, pharmacoepidemiology studies, nonclinical data, and pharmacovigilance data.

   Committee Discussion: *The majority of committee members agreed that a CV safety signal may exist for tegaserod; but the overall strength of the signal was weak, if present at all. Several members of the committee expressed concern that the CV safety signal detected in the adjudicated, pooled analysis of 29 placebo-controlled trials of tegaserod could result in CV events with use in a broader patient population. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss other potential safety concerns, including psychiatric safety adverse events of completed suicide and suicidal ideation/behavior, when considering reintroduction of tegaserod to the U.S. market.

   Committee Discussion: *The majority of committee members agreed that a weak psychiatric safety signal for adverse events of suicidal ideation/behavior and completed suicides was present in the clinical trial data. Several committee members recommended the addition of a warning in the label for tegaserod to appropriately communicate relevant safety concerns to patients and providers. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Is the reintroduction of tegaserod to the U.S. market supported by the available safety data? Discuss your answer.

   Vote Result: Yes: 11 No: 1 Abstain: 0

   Committee Discussion: *The majority of committee members agreed that reintroduction of tegaserod to the U.S. market was supported by the available safety and efficacy data. Committee members noted that clinical trial data showed tegaserod is effective in the treatment of IBS-C. Committee members also acknowledged that there are weak CV and psychiatric safety signals but agreed that these could be addressed by labeling. One of the panel members voted against the reintroduction of tegaserod to the U.S. in light of the CV and neuropsychiatric safety signals observed in the clinical trials, but stated he would change his vote if the signals were prominently described in labeling. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Do you agree that the therapeutic gain (treatment difference between tegaserod and placebo patients) is generally similar in magnitude between the severely symptomatic and originally approved population? Discuss your answer.

   Vote Result: Yes: 12 No: 0 Abstain: 0

   Committee Discussion: *The committee unanimously agreed that the therapeutic gain is generally similar in magnitude between the severely symptomatic and originally approved population. Please see the transcript for details of the committee discussion.*

5. **VOTE:** In which patient population would you expect the benefits to outweigh the risks for patients treated with tegaserod?

   A. IBS-C females
   B. IBS-C females at low CV risk
   C. IBS-C females who are severely symptomatic
   D. IBS-C females at low CV risk and who are severely symptomatic
   E. Other

   Discuss your answer.

   Vote Result: A: 1 B: 7 C: 0 D: 3 E: 1

   Committee Discussion: *The majority of the committee members favored the use of tegaserod in the population of IBS-C females at low CV risk, citing the unmet need of treatment options for this disease state and associated debilitating quality-of-life issues, and difficulties in defining IBS-C severity. Members also expressed the importance of a risk-benefit discussion between patient and provider prior to use of Zelnorm. Three committee members recommended that tegaserod be limited to females with IBS-C with low CV risk and who are severely symptomatic, due to concerns regarding the CV and psychiatric safety signals observed in clinical trials. One member of the committee voted for the broadest indication of females with IBS-C due to the difficulties in consistently defining IBS-C severity and the fluctuating nature of disease symptoms. One committee member recommended that tegaserod be limited to females with IBS-C who have low CV and low psychiatric risk, and are experiencing severe IBS-C symptoms. Please see the transcript for details of the committee discussion.*

   Some committee members discussed how best to define low CV risk in labeling, supporting a limitation to the treatment of adult women less than 65 years of age with IBS-C and no history of myocardial infarction or stroke.

The meeting was adjourned at approximately 3:50 p.m.