

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Gastrointestinal Drugs Advisory Committee
October 18, 2018**

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

Topic: The committee discussed new drug application (NDA) 210166 for prucalopride tablets for oral administration, submitted by Shire Development, LLC, proposed for the treatment of chronic idiopathic constipation in adults.

These summary minutes for the October 18, 2018 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on November 13, 2018.

I certify that I attended the October 18, 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 18, 2018

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 18, 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 Shire Development, LLC. 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 50 people in attendance. There were eight 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 new drug application (NDA) 210166 for prucalopride tablets for oral administration, submitted by Shire Development, LLC, proposed for the treatment of chronic idiopathic constipation in adults.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting): Joy McVey Hugick, BA (Consumer Representative); Sandeep Khurana, MBBS; Jennifer C. Lai, MD, MBA; Benjamin Lebwohl, MD, MS; Jean-Pierre Raufman, MD

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

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

Temporary Members (Voting): Sally Hunsberger, PhD; Sabrina Numann (Patient Representative); Steven F. Solga, MD; John Teerlink, MD; Udho Thadani, MD

FDA Participants (Non-Voting): Victor Crentsil, MD, MHS; Joyce Korvick, MD, MPH; Juli Tomaino, MD; Charles Line, MD; Ling Lan, PhD; Joel Weissfeld, MD, MPH

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

Open Public Hearing Speakers: Varuna Srinivasan, MD (National Center for Health Research); Ellen Stein, MD (Johns Hopkins Bayview Gastroenterology and Hepatology); Baha Moshiree, MD, MSc (statement read by Ellen Stein, MD); William Hasler, MD (American Neurogastroenterology and Motility Society); Brad Conway (American College of Gastroenterology); Trent Nichols Jr, MD (Quietmind Foundation); Jeffrey Roberts, MEd, BSc (IBS Patient Group); Jessica Roth (American Gastroenterological Association)

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

Juli Tomaino, 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

Shire Development, LLC

Introduction

Sunil Kadam, PhD
Senior Director, Global Regulatory Affairs
Shire

Unmet Need in Chronic Idiopathic
Constipation

Michael Camilleri, MD
Gastroenterologist and Professor of Medicine,
Pharmacology, and Physiology
Mayo Clinic

Prucalopride Efficacy Results

Heinrich Achenbach, MD
Global Clinical Development Team Lead
Shire

Prucalopride Safety

John Caminis, MD
Therapeutic Area Head, Global Drug Safety
Shire

Clinical Perspective on Prucalopride

Jan Tack, MD, PhD
Professor of Medicine
Head of Clinic, Department of Gastroenterology
University Hospital KU Leuven

Concluding Remarks

Debra Silberg, MD, PhD
Therapeutic Area Head, VP of Clinical Development
Shire

Clarifying Questions to the Presenters

BREAK

FDA PRESENTATIONS

Nonclinical Safety Findings of Prucalopride	Babatunde Emmanuel Akinshola, PhD Pharmacologist DGIEP, ODE III, OND, CDER, FDA
Clinical Pharmacology Findings of Prucalopride for Treatment of Chronic Idiopathic Constipation (CIC)	Shen (Steven) Li, PhD Clinical Pharmacology Reviewer Division of Clinical Pharmacology III Office of Clinical Pharmacology Office of Translational Sciences (OTS), CDER, FDA
Analysis of Prucalopride Efficacy Data for the CIC Program	Ling Lan, PhD Statistical Reviewer Division of Biometrics III Office of Biostatistics, OTS, CDER, FDA
Safety Evaluation of the Clinical Trial Data for the CIC Program	Charles Line, MD Medical Officer DGIEP, ODE III, OND, CDER, FDA
Assessment of Study 802, A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort	Joel Weissfeld, MD, MPH 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 and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Do the clinical trial data provide substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC)? Discuss your answer.

Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that the clinical trial data provides substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC). Please see the transcript for details of the committee discussion.*

2. **VOTE:** Has the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC been adequately addressed by the Applicant? Discuss your answer.

Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC has been adequately addressed by the Applicant. Members of the committee cited that the nonclinical data, selectivity of the drug for 5-HT₄ receptor, adjudicated, pooled cardiovascular safety analysis from 19 randomized, placebo-controlled clinical trials and lack of cardiovascular safety signal with extensive use of prucalopride in other countries as reasons for their approval. Please see the transcript for details of the committee discussion.*

- a. **DISCUSSION:** If you answered NO to Question #2, what additional safety data do you recommend? Discuss your answer.

Committee Discussion: *This sub-question is not applicable.*

3. **VOTE:** Does the risk-benefit profile of prucalopride support the approval of this application? Discuss your answer.

Vote Result: **Yes: 10** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that the risk-benefit profile of prucalopride supports the approval of this application. Several members of the committee expressed concern regarding the neuropsychiatric events that occurred in patients treated with prucalopride. Given the increased predisposition of CIC patients to neuropsychiatric issues such as depression, members of the panel recommended the addition of a warning in the label detailing relevant neuropsychiatric issues. Some committee members also suggested a long-term epidemiological study for further evaluation of a potential suicidality signal. One member of the committee was concerned about the potential long-term carcinogenic effects related to prucalopride. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 2:25 p.m.