Summary Minutes of the
Gastrointestinal Drugs Advisory Committee (GIDAC)
November 5, 2010
Hilton Washington DC/North
The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland

All external requests for the meeting transcript should be submitted to the CDER, Freedom of Information office.

These summary minutes for the Gastrointestinal Drugs Advisory Committee meeting of the Food and Drug Administration were approved November 30, 2010.

I certify that I attended the November 5, 2010 meeting of Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kristine Khuc, Pharm.D.
Designated Federal Official, GIDAC

_____/s/_____
Jean-Pierre Raufman, M.D.
Committee Chair, GIDAC

FOOD AND DRUG ADMINISTRATION (FDA)

Gastrointestinal Drugs Advisory Committee (GIDAC)

Hilton Washington DC/North

Gaithersburg, Maryland

November 5, 2010

Summary Minutes

The following is an internal report which has not been reviewed. A verbatim transcript will be available in about 4 weeks, sent to the Division of Gastroenterology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm195280.htm

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The Gastrointestinal Drugs Advisory Committee (GIDAC) met on November 5, 2010 at the Hilton Washington DC/North, The Ballrooms, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and Sponsor. The meeting was called to order by Jean-Pierre Raufman, M.D., (Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Official). There were approximately 100 persons in attendance. There were no speakers for the Open Public Hearing session.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting):
Garnet Andereson, Ph.D., Ronal Fogel, M.D., William Hasler, M.D., Atul Kumar, M.D., Jean-Pierre Raufman, M.D. (Chair), Jill Sklar (Consumer Representative), Steven Solga, M.D.

Temporary Member (Non-Voting):
Brahm Goldstein, M.D. (Acting Industry Representative)

Special Government Employee Consultants Present (Temporary Voting Members):
Shrikant Bangdiwala, Ph.D., Gregory Kearrns, Pharm.D., Ph.D., Jenifer Lightdale, M.D., Diane MacKinnon (Patient Representative), David Madigan, Ph.D., Richard Martin, M.D., Daniel Notterman, M.D., Alexander Rakowsky, M.D., Michael Reed, Pharm.D., Geoffrey Rosenthal, M.D., Ph.D., Colin Rudolph, M.D., Ph.D., Pamela Russell, M.D., Victor Santana, M.D.

Speakers (Non-Voting/Presenting Only):
Eric Hassall, MBChB, Susan Orenstein, M.D., FACG

FDA Participants Present (Non-Voting):
Laurie Burke, R.Ph., M.P.H., Elizabeth Durmowicz, M.D., Donna Griebel, M.D., Joyce Korvick, M.D., Amy Taylor, M.D., John Troiani, M.D., Ph.D.

Designated Federal Official:
Kristine Khuc, Pharm.D.

Issue: The Committee discussed results from clinical trials of proton pump inhibitors in gastroespohageal reflux disease (GERD) in patients less than one year of age, performed in response to a Pediatric Written Request under the Best Pharmaceuticals for Children Act (Nexium, esomeprazole by AstraZeneca LP; Prevacid, lansoprazole by Takeda Pharmaceuticals North America, Inc; Protonix, pantoprazole by Pfizer, Inc.) and Pediatric Research Equity Act (PREA) commitment (Prilosec, omeprazole by AstraZeneca LP). The pathophysiology (disease process) of GERD, its diagnosis and management, and issues related to the design of clinical trials in this age group was considered.

The Agenda was as follows:

Call to Order at 8:00 a.m. Introduction of Committee	Jean-Pierre Raufman, M.D. Chair, GIDAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, GIDAC
FDA Opening Remarks	Joyce Korvick, M.D. Deputy Director for Safety DGP (Division of Gastroenterology Products), CDER, FDA

FDA Presentation

Regulatory Background	Ali Niak, M.D. Medical Officer, DGP, CDER, FDA

Honorary Speakers

Infant GERD Pathophysiology Diagnosis I-GERQ Survey Instrument	Susan R. Orenstein, M.D., FACG (Speaker) Pediatric Gastroenterology Professor Emerita, Pediatrics University of Pittsburgh School of Medicine Pittsburgh, PA
Management	Colin D. Rudolph, M.D., Ph.D. (Speaker and Discussant) Division Chief Pediatric Gastroenterology and Nutrition Children's Hospital of Wisconsin & Medical College of Wisconsin Wauwatosa, WI

Safety	Eric Hassall, MBChB, FRCPC, FACG (Speaker) Professor of Pediatrics Division of Gastroenterology BC Children's Hospital & University of British Columbia Vancouver, BC, Canada
Clinical Pharmacology	Gregory L. Kearns, PharmD, Ph.D. (Speaker and Discussant) Professor of Pharmacology University of Missouri Kansas City, MO

Questions to Presenters

BREAK

Presentations of Trials by Sponsors: Lessons Learned

Evaluating Lansoprazole in Infant GERD: Challenges and Responses	Debra Markmann, Ph.D. Sr. Director, Chief Scientific Officer's Office Takeda Pharmaceuticals International, Inc.
FDA Advisory Committee on Infant GERD Research Biotherapeutics Lessons Learned from Protonix (Pantoprazole Sodium) Studies in Infant GERD	Gail Comer, M.D., Sr. Director, Medical Research, Research Biotherapeutics Pfizer, Inc.
AstraZeneca's Experience Related To PPI Clinical Studies in Patients <1 year of Age with GERD	Marta Illueca, M.D., FAAP Diplomate of the American Sub-Board of Pediatric Gastroenterology Executive Director, Clinical Development AstraZeneca, LP Harland Winter, M.D. Associate Professor of Pediatrics Harvard Medical School Former President, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)

FDA Presentation

Comparative Summary of Trials	John Troiani, M.D., Ph.D. Medical Officer GDP, CDER, FDA

Questions to Sponsors and FDA about trials

LUNCH

Committee Discussion and Questions

ADJOURN

Questions to the Committee:

1. Is the pathophysiology of GERD (gastroesophageal reflux disease) the same in patients ages 1 month to less than one year and adults? Please discuss.

The Chair took an unofficial vote for this question and the results were 4 "Yes", 14 "No", 3 "Abstain".

The Committee members had challenges in coming to a consensus on this question based on trying to differentiate and define GER and GERD in this particular patient population.

Committee members commented on the following:

- *Pathogenesis of symptoms is different*
- *Biggest difference between adults and infants is non verbal ability and in infants these symptoms are non-specific*
- *Looking at milk allergy as a disease by itself*
- *Biomarkers for reflux esophagitis*

(Please see official transcript for details)

2. When acid suppressing agents are approved for symptomatic GERD in adults, should studies in pediatric patients ages 1 month to less than 1 year be required? Please discuss.

The Chair took an unofficial vote for this question and the results were 19"Yes", 1"No", 1"Abstain".

Committee members commented on the following:

- *Explore the gut flora effects*

- *Target highly specific subset of patients (i.e. cystic fibrosis, underlying neurological disease, congenital esophageal lesions) and define dose*
- *Explore genomic aspects*
- *Increase public knowledge of current efficacy studies*
- *Need to perform safety and pharmacodynamic (PD)/pharmacokinetic(PK) studies*

(Please see official transcript for details)

3. Is there a population of infants that should be studied in future clinical trials of acid suppressing agents? Please discuss.

If you answered yes, please respond to the following questions:

a. How would this population be identified?

The committee members identified that the studies should be conducted in infants with neurological impairment, cystic fibrosis, esophageal altresia, airway related disease, intensive care infants with microaspiration, tracheal esophageal fistula, and erosive esophagitis.

b. What primary endpoint should be studied? What assessment tools (pH-metry, endoscopy, impedance, survey instruments) would you recommend to assess the primary endpoint?

A majority of the committee members agreed that pre and post endoscopy should be explored. In addition, they also agreed that pH-metry, endoscopy, and survey instruments may be used. There is also a need to obtain data on post-treatment repeated endoscopies. Suction Biopsy was mentioned, but may not be practical. More guidance may be needed on performing biopsy in this patient population. Liver cytochrome enzyme measurements should also be investigated.

c. What design should be used? Please comment on duration of treatment and the roles of enrichment, withdrawal, and concomitant therapies (H_2 blockers, antacids, conservative measures).

Some Committee members recommended:

- *Placebo controlled, randomized trial with targeted population;*
- *Lead-in phase with lifestyle modifications (i.e. hypoallergenic diet, avoidance of tobacco smoke) of 4 weeks before entry of study with duration of approximately 3 months;*
- *No withdrawal;*

- *Concomitant therapies would be precluded;*
- *Continuation of conservative measures.*

(Please see official transcript for details)

4. Are your recommendations in response to the questions above applicable to the neonatal and premature infant population? Please discuss.

The majority of the committee members remarked that this population is unique and the existing PK and PD data are not applicable to this subset. Discussions involved the issue around airway problems, apnea with this population and the use of PPIs for these conditions.

(Please see official transcript for details)

5. In what indications other than GERD in patients 1 month to less than 1 year might acid suppressing agents have a therapeutic role? Please discuss.

Committee members commented that there are very limited indications other than GERD. These limited indications include: peptic ulcer disease, airway disease, and Helicobacter pylori management.

(Please see official transcript for details)

Meeting adjourned at approximately 4:05 p.m.