Summary Minutes of the
Gastrointestinal Drugs Advisory Committee (GIDAC)
November 4, 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 4, 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 4, 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 4, 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):
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., Srinivasan Dasarathy, M.D., David Fox, M.D., Diane MacKinnon (Patient Representative), David Madigan, Ph.D., Nancy Olsen, M.D., David Pisetsky, M.D., Ph.D.,

Regular Government Employee Present(Temporary Non-Voting Member):
David Graham, M.D.

Speaker (Non-Voting/Presenting Only):
Denis McCarthy, M.D., Ph.D.

FDA Participants Present (Non-Voting):
Eric Brodsky, M.D., Donna Griebel, M.D., Sharon Hertz, M.D., Joyce Korvick, M.D., Anil Nayyar, M.D.

Designated Federal Official:
Kristine Khuc, Pharm.D.

Issue: The Committee discussed the adequacy of endoscopically documented gastric ulcers as an outcome measure to evaluate drugs intended to prevent gastrointestinal complications of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin.

The Agenda was as follows:

Call to Order at 8:00 a.m. Introduction of Committee	Jean-Pierre Raufman, M.D. Acting Chair, GIDAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, GIDAC
FDA Opening Remarks	Donna Griebel, M.D. Director Division of Gastroenterology Products CDER, FDA
Sponsor Opening Remark	Jeffrey Sherman, M.D. Chief Medical Officer Horizon Pharma, Inc.
Sponsor Presentations	
NSAID-Associated GI Tract Injury and Current Therapies for Reduction of NSAID-Associated GI Tract Injury	Loren A. Laine, M.D. Professor of Medicine Gastrointestinal and Liver Diseases Division Associate Chair of Medicine Keck School of Medicine University of Southern California
Clinical Relevance of Endoscopic Ulcers	Andrew Moore, Ph.D. Pain Research and Nuffield Department of Anesthetics University of Oxford Honorary Professor School of Health Sciences University of Wales Swansea

History of Upper Gastrointestinal (UGI) Endoscopy and Outcome Trials in Current Assessments of NSAID-Induced UGI Injury	Lawrence Goldkind, M.D. Assistant Professor of Medicine Uniformed Services University of Health Sciences Attending Staff, Division of Gastroenterology National Naval Medical Center

Questions to the Sponsor

Break

Speaker Presentation

Predicting GI Complications of NSAID Therapy- Use of Surrogates and Outcomes	Denis McCarthy, M.D. (Speaker) Professor of Medicine and Biochemistry University of New Mexico School of Medicine Gastroenterologist Raymond G. Murphy Veterans Affairs Medical Center

Questions to the Presenter

FDA Presentations

Efficacy Endpoints for NSAID-Associated Upper GI Injury	Anil Nayyar, M.D. Medical Officer Division of Gastroenterology Products CDER, FDA
Cross Study Comparisons of Endoscopically-Diagnosed Ulcers vs. Upper GI Complications (UGICs)	Eric Brodsky, M.D. Medical Officer CDER, FDA

Questions to the FDA

Lunch

Committee Discussion and Questions

Adjournment

Questions to the Committee:

Products: Misoprostol, H2RAs (Histamine-2 Recepter Antagonist), PPIs (Proton Pump Inhibitor)

1. Are endoscopically-diagnosed gastric/duodenal ulcers an adequate primary efficacy endpoint for evaluating products intended to prevent NSAID-associated upper GI toxicity? Please explain your vote and if you vote no, please recommend an appropriate endpoint and study design (e.g., patient population). (Vote: Yes, No, Abstain)

Yes: 8 No: 4 Abstain: 1

The Committee members questioned the meaning of the word "adequate" in this context.

Committee members who voted "Yes" felt that this is not a perfect endpoint and suggested the following:

- *Patient population studied to include elderly patients;*
- *Further look into Helicobacter pylori prevalence;*
- *Performing studies of different NSAIDS with different mechanisms of action;*
- *Defining indication for doing endoscopy;*
- *Improvement and standardization of measurement mechanisms (i.e. ulcer depth, video imaging) and timing assessments;*
- *Need for more comparator trials.*

Committee members who voted "No" also emphasized reproducibility and standardization concerns and suggested bleeding as a clinically significant endpoint.

(Please see official transcript for details)

2. Given that:
-endoscopy trials of misoprostol and PPIs in patients at risk of NSAID-associated upper GI toxicity have demonstrated a decreased relative risk (RR) in endoscopically-diagnosed ulcers compared to control of between 0.2 to 0.4, and a 10 to 40% absolute risk difference, and

-in an esomeprazole endoscopy trial that enrolled patients receiving low dose aspirin (81 to 325 mg daily) as prophylaxis for cardiovascular protection, the decreased relative risk (RR) in endoscopically-diagnosed ulcers compared to control was 0.3, but the absolute risk difference was 3%,

How should a clinically meaningful difference in endoscopically-diagnosed ulcers be defined? Please address the type of analysis(es) and magnitude of difference in your answer.

The overall consensus of the committee is that the relative risk (RR) reduction is clinically meaningful, but there is still the question as to whether endpoints are clinically significant.

Committee members commented that there is a need to:

- *Create a risk score;*
- *Design different endpoints for different subset populations;*
- *Reflect absolute risk reduction rather than relative risk in drug label;*
- *Obtain video rather than static imaging;*
- *Define the risks by the patient population;*
- *Not extrapolate data from a low risk to high risk group or vice versa;*
- *Evaluate bleeding events which is a major complication.*

(Please see official transcript for details)

3. For the products discussed in Question 1, discuss the appropriate duration of endoscopy trials.

The majority of the committee agreed that a 3 to 6 month period for studies is reasonable. There were also comments regarding the quantity of studies and to perform longer studies for safety reasons.

(Please see official transcript for details)

Products: NSAIDs

4. Are endoscopically-diagnosed gastric/duodenal ulcers an adequate endpoint for evaluating NSAID-associated upper GI toxicity in NSAID product development? Please explain your vote and if you vote no, please recommend an appropriate endpoint and study design (e.g., patient population). (Vote: Yes, No, Abstain)

Yes: 4 **No: 8** **Abstain: 1**

The Committee members questioned the meaning of the word "adequate" in this context.

For those who voted "Yes", they felt that most toxicities were in the upper GI tract and would be sufficiently captured by endoscopy.

Committee members who voted "No" had concerns regarding mechanism of action and concerns of safety and addressing global GI toxicities. Those members indicated that evaluating 'endoscopically-diagnosed gastric/ duodenal ulcers' would be a good first step as a screen to identify drugs that have unacceptable GI toxicity. To ensure safety, drugs that passed this first screening 'test' would still require further measures (i.e. bleeding events). In addition, they also recommended that outcome studies would be relevant.

(Please see official transcript for details)

Questions 5 and 6 were not addressed*

5. If you think that endoscopically-diagnosed gastric/duodenal ulcers is an acceptable endpoint for the products discussed in Question 4, can a clinically meaningful difference be defined a priori? Please address the type of analysis(es) and magnitude of difference in your answer. (Vote: Yes, No, Abstain)

6. For the products discussed in Question 4, discuss the appropriate duration of endoscopy trials.

*Question was reframed for the Committee to discuss what would be an important feature of an outcome study in terms of evaluating the safety of an NSAID.

Committee members commented on evaluation of bleeding events (i.e. measuring stool hemoglobin using HemoQuant, actual bleeding event with endpoints of 6 to 12 months).

(Please see official transcript for details)

Products: Misoprostol, H2RAs, PPIs, NSAIDs

7. If endoscopically-diagnosed gastric/duodenal ulcers is not an adequate primary endpoint for the products discussed in Questions 1 or 4, please discuss the type of evidence that is needed to establish this endpoint for use in future registration trials.

Some Committee members commented:

- *A rigorous study be undertaken to evaluate and reduce intra- and inter-observer variability when defining an ulcer;*
- *Look at progression of ulcer over time (i.e. ulcer size,) and effect of intervention;*
- *Look at dyspepsia as an outcome measure;*
- *Have an independent group validate trials;*
- *Advantage of video versus static imaging.*

(Please see official transcript for details)

Meeting adjourned at approximately 3:40 p.m.