

**Summary Minutes of the
Gastrointestinal Drugs Advisory Committee (GIDAC)
Hilton Washington DC/Silver Spring, Silver Spring, Maryland**

July 21, 2011

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 on 8/4/11.

I certify that I attended the July 21, 2011 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 Officer,
GIDAC**

_____/s/_____
**William Hasler, M.D.
Acting Committee Chair,
GIDAC**

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
Gastrointestinal Drugs Advisory Committee (GIDAC)
Hilton Washington DC/Silver Spring, Silver Spring, Maryland
July 21, 2011
Summary Minutes

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the FDA, Center for Drug Evaluation and Research, met on July 21, 2011 at the Hilton Washington DC/Silver Spring, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Centocor Ortho Biotech, Inc. The meeting was called to order by William Hasler, M.D., (Acting Chair), and the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Officer). There were approximately 120 people in attendance. There were 2 Open Public Hearing speakers.

Issue: The Committee discussed the results from a clinical trial of supplemental Biologics License Application (sBLA) 103772/5301 Infliximab, REMICADE, by Centocor Ortho Biotech, Inc., in the treatment of pediatric patients with moderately to severely active ulcerative colitis.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting):

Anderson, Garnet, Ph.D., William Hasler, M.D. (Acting Chair), Jill Sklar (Consumer Representative)

Gastrointestinal Drugs Advisory Committee Members Not Present (Voting):

Ronald Fogel, M.D., Atul Kumar, M.D., Jean-Pierre Raufman, M.D., Steven Solga, M.D.

Gastrointestinal Drugs Advisory Committee Member Present (Non-Voting):

Debra Silberg, M.D., Ph.D. (Industry Representative)

Temporary Members (Voting):

Steven J. Czinn, M.D., Richard Grand, M.D., Thomas Gross, M.D., Ph.D., Colleen Hadigan, M.D., David J. Keljo, M.D., Ph.D., Ed Morawetz (Patient Representative), Michael A. Narkewicz, M.D., Rachel Rosen, M.D., Victor Santana, M.D., John Snyder, M.D., Carolyn Sullivan, M.D., Anne Zajicek, M.D., Pharm.D.

FDA Participants (Non-Voting):

Mark Avigan, M.D., Robert Fiorentino, M.D., M.P.H., Donna Griebel, M.D., Jessica Lee, M.D., M.M.Sc., Nitin Mehrotra, Ph.D.

Designated Federal Officer:

Kristine Khuc, Pharm.D.

Open Public Hearing Speakers:

Nick Uzl, Digestive Disease National Coalition (DDNC)
Sandra C. Kim, M.D., Crohn's and Colitis Foundation of America (CCFA)

The agenda proceeded as follows:

Call to Order
Introduction of Committee

William Hasler, M.D.
Acting Chair, GIDAC

Conflict of Interest Statement

Kristine Khuc, Pharm.D.
Designated Federal Officer, GIDAC

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Open Public Hearing

Committee Discussion and Questions to the Committee

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Questions to the Committee:

1. Is it reasonable to assume that the course of ulcerative colitis and its response to treatment in adult and pediatric patients are sufficiently similar to be able to extrapolate efficacy from adult to pediatric patients for:

a. Induction of clinical remission? (Vote)

YES: 15

NO: 0

ABSTAIN: 0

***Committee Discussion:** The committee unanimously agreed that there was sufficient and well supported data to extrapolate from adult to pediatric patients for the induction of clinical remission.*

b. Maintenance of clinical remission? (Vote)

YES: 12

NO: 3

ABSTAIN: 0

***Committee Discussion:** The overall majority of the committee agreed that the disease course is similar and appropriate to extrapolate efficacy from adults to pediatrics for the maintenance of clinical remission. The minority of the committee members who voted “No” had concerns in the number of drop-outs and the low number of patients in remission at the end of the study.*

c. Induction of mucosal healing? (Vote)

YES: 13

NO: 2

ABSTAIN: 0

***Committee Discussion:** The majority of the committee members who voted “Yes” remarked that extrapolation from the adult to pediatric patient population is reasonable because the disease process is similar in these groups of patients. Those committee members who voted “No” commented that there was insufficient data on mucosal healing and that the data was not robust at anytime during the trial.*

d. Maintenance of mucosal healing? (Vote)

YES: 8

NO: 6

ABSTAIN: 1

***Committee Discussion:** The committee members who voted “Yes” commented that although children may develop more severe disease, there are similarities in the disease process between the adult and pediatric population that allow for extrapolation. The committee members who voted “No” questioned whether ulcerative colitis mucosal healing is the same in adult versus pediatric patients and had concerns relating to endoscopy and insufficient data. One committee member abstained based on her lack of clinical expertise. It is noted that a panel member placed a vote in the electronic*

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4. Assuming extrapolation is appropriate, do the pediatric data support the dosing for the proposed pediatric indications of:

- a. induction of mucosal healing (5 mg/kg IV at 0, 2 & 6 weeks)? (Vote)

YES: 13

NO: 2

ABSTAIN: 0

***Committee Discussion:** The overall majority of the committee agreed that the data presented was adequate for the proposed pediatric indication of induction of mucosal healing at a dose of 5 mg/kg IV at 0, 2, & 6 weeks. The minority voted who “No” remarked that there was insufficient data. It is noted that a panel member placed a vote in the electronic voting system as “NO”; however, the panel member verbally stated his vote as “YES”. The Chair stated for the record that the vote is 14 “YES”, 1 “NO”, and 0 abstention.*

- b. maintaining mucosal healing (5 mg/kg IV every 8 weeks)? (Vote)

YES: 5

NO: 10

ABSTAIN: 0

***Committee Discussion:** The majority of the committee members who voted “No” agreed that there was inadequate and unconvincing data to support the proposed pediatric indication of maintaining mucosal healing at a dose of 5 mg/kg IV every 8 weeks. While others who voted “Yes” also acknowledged that the data was very limited and that the study was not powered to evaluate maintenance of mucosal healing.*

- c. eliminating corticosteroid use (5 mg/kg IV 0, 2, & 6 weeks, then every 8 weeks)? (Vote)

YES: 2

NO: 13

ABSTAIN: 0

***Committee Discussion:** An overwhelming majority voted “No” and commented that the data was inadequate for eliminating corticosteroid use if the drug product is dosed at 5 mg/kg IV 0, 2, & 6 weeks, then every 8 weeks. The minority that voted “Yes” remarked that there was reasonable data on the assumption that 38% were off corticosteroids.*

Please see the transcript for details of the committee’s discussions.

5. In light of the pediatric safety data provided in T72, the post-marketing safety analyses, and the pharmacokinetic (PK) and exposure response data, are there safety concerns that have not been adequately addressed? (Vote)

YES: 14

NO: 1

ABSTAIN: 0

- If yes, what additional safety data should be collected?
Discuss whether this data should be collected prior to or post approval.

***Committee Discussion:** An overwhelming majority of the committee members concurred that there are safety concerns that have not been adequately addressed, and suggested that additional information be collected regarding: dose escalation, immunogenicity, malignancy, long term cumulative exposure. They also strongly emphasized the need for better patient education, informed consent, counseling, and provider education using a more modern technological approach. The committee member who voted “No” and expressed that there is still a need for more post-hoc data analyses.*

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Please see the transcript for details of the committee's discussion.

6. Does the benefit:risk profile support approval of Remicade for the pediatric UC indications of:

a. Induction of clinical remission? (Vote)

YES: 14 NO: 0 ABSTAIN: 0 NO VOTE: 1

***Committee Discussion:** The committee unanimously voted "Yes" and agreed that there is a favorable benefit to risk ratio that support approval of Remicade for induction of clinical remission in pediatrics. It is noted that one committee member left the meeting at approximately 2:45 PM, and thus there is one "No Vote" recorded.*

b. Maintenance of clinical remission? (Vote)

YES: 10 NO: 3 ABSTAIN: 1 NO VOTE: 1

***Committee Discussion:** The overall majority of the committee voted "Yes" in favor of an approval of Remicade for maintenance of clinical remission in pediatrics. The committee members who voted "No" voiced concerns regarding long term safety and possible resurgence of combination therapy for this population. One member abstained and remarked that although there is clear induction of clinical remission, the data for maintenance of clinical remission is limited and unclear. It is noted that one committee member left the meeting at approximately 2:45 PM, and thus there is one "No Vote" recorded.*

c. Induction of mucosal healing? (Vote)

YES: 13 NO: 1 ABSTAIN: 0 NO VOTE: 1

***Committee Discussion:** The committee unanimously voted "Yes" that there was demonstration of induction of mucosal healing. It is noted that a panel member placed a vote in the electronic voting system as "NO"; however, the panel member verbally stated her vote as "YES". The chair stated for the record that the vote is 14 "YES", 0 "NO", and 0 abstention. Additionally, it is noted that one committee member left the meeting at approximately 2:45 PM, and thus there is one "No Vote" recorded.*

d. Maintenance of mucosal healing? (Vote)

YES: 5 NO: 8 ABSTAIN: 1 NO VOTE: 1

***Committee Discussion:** The overall majority of the committee voted "No" and emphasized that the data was not strong enough to support the approval of Remicade for maintenance of mucosal healing in pediatrics. Those who voted "Yes" based their decision on the assumptions of extrapolation from adult data. One member abstained from voting and raised the concern that there are no long term safety data. It is noted that one committee member left the meeting at approximately 2:45 PM, and thus there is one "No Vote" recorded.*

e. Eliminating corticosteroid use? (Vote)

YES: 2 NO: 12 ABSTAIN: 0 NO VOTE: 1

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Committee Discussion: *The overall majority voted “No” and noted that the data was insufficient for extrapolation of the adult data to pediatrics. The committee members who voted “Yes” opined that the risks did not overwhelm the benefits and that data on 38% of patients off corticosteroids was convincing. It is noted that one committee member left the meeting at approximately 2:45 PM, and thus there is one “No Vote” recorded.*

Please see the transcript for details of the committee’s discussions.

7. (Based on the discussions that transpired at the meeting, the FDA added the following question) If approved at the 5 mg/kg dose, how would clinicians use Remicade, would the dose be increased to 10 mg/kg if there is inadequate response to the 5 mg/kg dose, and what parameters would be monitored?

Committee Discussion: *One committee member commented that there may be increases in usage of this drug in moderate UC and that this practice may already be happening. The concern is that it may be used more frequently under sub-optimal circumstances. Dose escalation is seen in Crohn’s Disease patients and this is done by adjustments in frequency intervals or slow to immediate titration of doses, but this is done without any idea of what the toxicity and consequences are.*

Please see the transcript for details of the committee’s discussion.

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