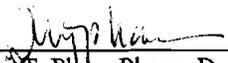


Summary Minutes of the Gastrointestinal Drugs Advisory Committee
January 23, 2008
Location: Hilton Washington DC Silver Spring, the Maryland Ballroom
8727 Colesville Road, Silver Spring, MD

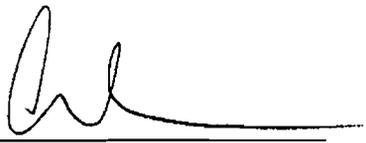
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the January 23, 2008 of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on 1/28/08

I certify that I attended the January 23, 2008, meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration meeting and that these minutes are accurately reflects what transpired.



Mimi F. Phan, Pharm.D., R.Ph.
Designated Federal Official



Alan L. Buchman, M.D., M.S.P.H.
Acting-Chair

Meeting of the Gastrointestinal Drugs Advisory Committee
January 23, 2008

Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and the sponsor. The meeting was called to order by Alan Lewis Buchman, M.D., M.S.P.H. (Acting-Chair); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D., R.Ph. (Designated Federal Official). There were approximately two hundred (200) persons in attendance. There were zero (0) speaker for the Open Public Hearing session.

Issue:

The committee discussed the safety and efficacy of new drug application (NDA) 21-775, ENTEREG (alvimopan), Adolor Corporation, for the proposed indication of acceleration of time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

Attendance:

GIDAC Committee Members Presenting (voting)

Alan L. Buchman, MD, MSPH (Acting Chair); Lin Chang, MD; Michael S. Epstein, MD; Pankaj J. Pasricha, MD.

Special Government Employee Consultants (Voting):

JoEllen Cokery-Deluca (Patient Representative); Joseph J. Cullen, MD; Sean P. Hennessy, PharmD, PhD; Judith M. Kramer, MD, MS; Alexander H. Krist, MD; Robert A. Levine, MD; Abraham Michael Lincoff, MD, FACC; Michael A. Proschan, PhD; Ronald Richardson, MD; Douglas R. Rosing, MD; Mark A. Talamini, MD.

FDA Participants (Non-Voting):

Julie G. Beitz, MD; Ruyi He, MD; Claudia Karwoski, PharmD; Joyce A. Korvick, MD, MPH; Joyce Weaver, PharmD, BCPS.

Designated Federal Official:

Mimi T. Phan, PharmD, RPh.

Open Public Hearing:

None

The agenda was as followed:

Call to Order

Alan L. Buchman, M.D., M.S.P.H.
Acting Chair, GIDAC

Conflict of Interest Statement

Mimi Phan, Pharm.D., R.Ph.
Designated Federal Official, GIDAC

Introduction/Background

Joyce A. Korvick, M.D., M.P.H.
Deputy Director
Division Gastroenterology Products,
CDER/FDA

SPONSOR PRESENTATIONS:

Entereg (Alvimopan) Capsules
Introduction

Linda Young, R.Ph., J.D.
Vice President of Regulatory Affairs
Adolor Corporation

Postoperative Ileus (POI)
A Surgical Perspective

Anthony Senagore, M.D., M.S., M.B.A.
Vice President, Research and Education
Spectrum Health, Grand Rapids, MI

POI Clinical Development and Efficacy

Lee Techner, D.P.M.
Senior Medical Director
Adolor Corporation

Study 014: Safety Findings

Eric Mortensen, M.D., Ph.D.
GlaxoSmithKline

POI Safety Risk Management

David Jackson, M.D.
Senior Vice President & Chief Medical
Officer
Adolor Corporation

Questions to the Sponsor

Break

FDA PRESENTATIONS:

Efficacy Data

Ruyi He, M.D.
Medical Team Leader
Division of Gastroenterology Products,
CDER/FDA

Safety Data

Marjorie Dannis, M.D.
Medical Reviewer
Division of Gastroenterology Products,
CDER/FDA

Non-Clinical Findings

Tamal Chakraborti, Ph.D.
Pharmacologist
Division of Gastroenterology Products,
CDER/FDA

Post-Marketing Safety and Risk
Minimization Action Plan

Joyce Weaver, Pharm.D., BCPS
Senior Drug Risk Management Analyst
Office of Surveillance and
Epidemiology, CDER/FDA

Questions to the FDA

Lunch

Open Public Hearing

Questions to the Committee and Recommendations

Break

Questions to the Committee and Recommendations

Adjourn

Questions to the Committee:

1. For the assessment of efficacy in clinical trials of post-operative ileus (POI), GI2 and GI3 have been utilized to measure times for recovery of upper and lower GI function. What do you consider a minimum acceptable treatment difference as measured by GI2 or GI3 for alvimopan relative to placebo? 12h? 24h? 36h? other?

The committee felt that either a 12 or 24 hours difference was considered to have a clinical efficacy. (Please refer to the transcripts for detailed discussions)

2. Do you consider the efficacy results from the submitted POI studies to be clinically meaningful? Explain which endpoints (GI2, GI3, DOW, Ready, other) and which studies you are relying on to support your conclusion.

Yes: 13

No: 0

Abstain: 2

The committee felt that GI2, where patient are ready to be discharge was the most important endpoint. (Please refer to the transcripts for detailed discussions)

3. Based on currently available data, do you have concerns for the use of alvimopan 12mg capsules in the short-term (i.e., 7 days or 15 doses) for patient following partial large or small bowel resection surgery with primary anastomosis with regard to the following:

The Agency requested the committee to vote on the cardiovascular events only.

- a. Cardiovascular events?

Yes: 8

No: 6

Abstain: 1

- b. Neoplastic events?
- c. Bone fractures?

The committee felt that there were some concerns for the cardiovascular risks, although these risks were not adequately addressed. The major concern was the patient follow-up was also inadequate. There was no data to support or denied for cumulative doses especially with repeated doses.

The majority of risk analysis was based on a single long-term study, and there appeared to be weak signals for all three problems. Thus, the cardiovascular, neoplastic and bone fractures risks cannot be discounted.

The committee expressed clearly that if the drug is approved, there should be a process to put in affect to monitor these potential side effects. (Please refer to the transcripts for detailed discussions)

4. Do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients following partial large or small bowel resection surgery with primary anastomosis?

Yes: 9

No: 6

Abstain: 0

There were some concerns with efficacy demonstrated in the trials, especially if the patients were not on opioids. However, the consensus of the committee was, there were real clinical benefits to early discharge and these studies demonstrated a moderate to marginal effect. A few members expressed a concern that these risks might be real, but the risks might not be applicable to short term use. (Please refer to the transcripts for detailed discussions)

5. If alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks? Explain what features of the proposal would be most desirable.

Yes: 0

No: 14

Abstain: 1

The unanimous decision of the panel was that the Risk management plan was inadequate. If the drug is approved, such risk management plan should be focus more specific to prevention of off-label uses. (Please refer to the transcripts for detailed discussions)

6. Based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short term and long term clinical studies of alvimopan?

There was consensus of the committee that a prospective study of long-term of adverse event would be necessary. The panel suggested 2 mechanisms: 1) a phase-4 trial to monitor the risk of the specific (cardiovascular, neoplastic and bone fractures) or other potential events or 2) to implement a more thorough follow-up in the future studies or potential indications. (Please refer to the transcripts for detailed discussion).

The meeting adjourned at 1615 hours.