Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Gastrointestinal Drugs Advisory Committee

Holiday Inn
8777 Georgia Ave., Silver Spring, MD

March 19, 2002

Members Present

M. Michael Wolfe, M.D., Chair
Nancy L. Geller, Ph.D.
Maria H. Sjogren, M.D.
Ronald Fogel, M.D.
Robert Alan Levine, M.D.
Susan Cohen
Joel Richter, M.D.
Michael Camilleri, M.D.
Byron Cryer, M.D.
John Thomas LaMont, M.D.
David Colin Metz, M.D.

Consultants

Scott Lippman, M.D.
Nancy A. Roach
Curt Furberg, M.D.

Guest Experts

Bernard Levin, M.D.
Alex Krist, M.D.
David F. Ransohoff, M.D.
David A. Lieberman, M.D.
John A. Baron, M.D.
Anil Rustgi, M.D.
Barry Kramer, M.D.
George S. Goldstein, M.D.

FDA Participants

Florence Houn, M.D
Mark Avigan, M.D.
Victor Raczkowski, M.D.
Rick Pazdur, M.D.

These summary minutes for the March 19, 2002 meeting of the Gastrointestinal Drugs Advisory Committee were approved on March 29, 2002.

I certify that I attended the March 19, 2002 meeting of the Gastrointestinal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

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M. Michael Wolfe, M.D.
Chair

This report contains public information that has not been reviewed by the agency or the Gastrointestinal Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 12 days. External requests should be submitted to the Freedom of Information office.

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met March 19, 2002 at the Holiday Inn, 8777 Georgia Ave., Silver Spring, MD

The committee discussed standards in study designs of clinical trials testing the efficacy and safety of chemopreventive agents that are being developed to gain FDA approval in reducing the risk of sporadic colorectal adenomatous polyps and sporadic colorectal cancer.

The Committee had received a briefing document from the FDA.

There were approximately 100 persons in the audience. The meeting was called to order at 8:00am by the Chair, M. Michael Wolfe, M.D. Thomas H. Perez, Executive Secretary of the Gastrointestinal Drugs Advisory Committee read the Meeting Statement. The Committee members and discussants introduced themselves.

The presentations began at 8:25 a.m. and proceeded as follows.

Epidemiology and Mechanisms of Colorectal Cancer
Anil K. Rustgi, M.D., T.Grier Miller Associate Professor of Medicine and Genetics; University of Pennsylvania

Colorectal Cancer Screening and Surveillance
David A. Lieberman, M.D., Chief, Division of Gastroenterology, Oregon Health Sciences University

Overview of Chemoprevention Trials
Bernard Levin, M.D., Vice President for Chemoprevention, Professor of Medicine, UTMD Anderson Cancer Ctr

Benefit and Risk Analysis for Chemoprevention of Sporadic Colorectal Cancer
Mark Avigan, M.D., C.M., Medical Officer, Division of Gastrointestinal and Coagulation Drug Products

The Open Public Hearing included six participants, and began at approximately 11:00 a.m.

Robert S. Sandler, M.D., consultant for Merk Pharmaceuticals
Priscilla Savary, Colorectal Cancer Network
Gary Gordon, M.D., National Cancer Institute
Ernie Hawk, M.D., National Cancer Institute
Gary Kelloff, M.D., National Cancer Institute

The meeting was reconvened after lunch at approximately 1 p.m.
Introduction to the Questions by Mark Avigan, M.D., and
Charge to the Committee by Victor F.C. Raczkowski, M.D.

A thorough discussion of the questions followed, and the meeting was adjourned at 4:40 p.m.

The Committee discussed the following questions to which no votes were requested or taken. The complete discussion will be made available through the verbatim meeting transcripts. The trascript will be posted on the FDA Webpage.

Questions for Gastrointestinal Drugs Advisory Committee
Chemoprevention of Sporadic Colorectal Cancer (CRC)
March 19, 2002

1) For individuals who are able and willing to undergo colonoscopic screening or surveillance, is either partial and/or complete suppression of colorectal adenomatous polyps a clinically meaningful benefit? Why or why not?

   If adenomatous polyp suppression is not a clinically meaningful benefit, what additional information would be needed to demonstrate that partial or complete suppression of polyps is of clinical benefit in such individuals?

2) A chemoprotective agent (CPA) that suppresses polyp growth may become resistant to drug effects. Additionally, it may preferentially allow small, invasive lesions to go undetected on colonoscopy while large, indolent lesions are identified and removed. If polyp suppression is used as an endpoint in clinical trials of a CPA:

   a) How long should the trial be?
   b) What should the time interval be between colonoscopic evaluations?
   c) What endpoints and follow up are needed to rule out possible resistance to drug effects? Differential identification and removal of large, indolent lesions?
   d) How should a rebound withdrawal effect be studied?

3) Given that mortality and invasive CRC incidence rates are gold standards for demonstrating clinical benefit, what is the relative importance of other study endpoints in clinical trials of CPAs, such as:

   a) Lengthening the interval between (or replacement of) colonoscopic screening or surveillance?
   b) Reduction in the number of procedural complications associated with polypectomies?
   c) Other clinically meaningful outcomes?

4) Should the results of clinical trials in individuals at high risk for CRC be generalized to individuals at normal risk for CRC? Why or why not? Please specify the criteria that should be used to classify risk in clinical trials of CPAs.

5) Should clinical trials of CPAs be required to include substantial numbers of individuals with particular demographic or baseline characteristics (e.g., age, race, sex) or on particular concomitant therapies (e.g., nonsteroidal anti-inflammatory agents)?

6) In randomized, placebo-controlled clinical trials of CPAs used as an adjunct to colonoscopic screening or surveillance, what would represent a clinically meaningful effect size for:
   a) Reduction of benign adenomas?
   b) Reduction of premalignant lesions?
   c) Reduction of colorectal cancer?
   d) Increase in the time interval between colonoscopies?
   e) Reduction of complications associated with polypectomies?

7) How should dropouts/censored patients be analyzed?

8) What is your advice concerning the safety evaluation of a drug proposed as a CPA in an at-risk population without active disease?

9) For partial or complete suppression of adenomatous polyps:
   a) Should the proportion of patients who experience the clinically meaningful benefit of polyp suppression exceed the proportion of patients who experience serious adverse events?
   b) If yes, should the study be powered accordingly? Why or why not?
   c) In order to ensure long term safety of CPAs, what should the length of the clinical trials be?