

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Pulmonary-Allergy Drugs Advisory Committee

June 13, 2005
620 Perry Parkway, Gaithersburg, Maryland

Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting):

Erik R. Swenson, M.D.
Mark L. Brantly, M.D.
Steven Gay, M.D., M.S.
Carolyn M. Kerckmar, M.D.
Fernando D. Martinez, M.D.
I. Marc Moss, M.D.
Lee S. Newman, M.D.
Calman P. Prussin, M.D.
Michael Schatz, M.D., M.S.
David A. Schoenfeld, Ph.D.

Pulmonary-Allergy Drugs Advisory Committee Consultants (voting):

Karen Schell, RRT (Consumer Representative)
Jacqueline S. Gardner, Ph.D., M.P.H.
Nancy J. Sander (Patient Representative)

Industry Representative (non-voting):

Theodore Reiss, M.D. was invited but unable to attend due to an urgent family matter.

Pulmonary-Allergy Drugs Advisory Committee Members Absent:

Peter E. Morris, M.D.
William J. Calhoun, M.D.

FDA Participants:

Robert Meyer, M.D.
Badrul Chowdhury, M.D.
Anne Trontell, M.D., M.P.H.
Eugene J. Sullivan, M.D., FCCP
Sally Seymour, M.D.
J. Harry Gunkel, M.D.

Open Public Hearing Speakers:

Chris Ward

Executive Secretary

Teresa A. Watkins

I certify that I attended the July 13, 2007 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Teresa A. Watkins
Executive Secretary, PADAC

Erik R. Swenson, M.D.
Chair, PADAC

Quick Minutes
Pulmonary-Allergy Drugs Advisory Committee Meeting
July 13, 2005

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at:

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

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA and Sponsors. The meeting was called to order by Erik R. Swenson (Chair, PADAC); the conflict of interest statement was read into the record by Mary Ann Killian, Program Integrity Officer. There were approximately 300 persons in attendance. There was 1 speaker for the Open Public Hearing Session (see below for a listing of the speaker).

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members Present (voting)

Erik R. Swenson, M.D., Mark L. Brantly, M.D., Steven Gay, M.D., M.S., Carolyn M. Kerckmar, M.D., Fernando D. Martinez, M.D., I. Marc Moss, M.D., Lee S. Newman, M.D., Calman P. Prussin, M.D., Michael Schatz, M.D., M.S., David A. Schoenfeld Ph.D..

Pulmonary-Allergy Drugs Advisory Committee Consultants (voting):

Karen Schell, RRT (Consumer Representative), Jacqueline S. Gardner, Ph.D., M.P.H., Nancy J. Sander (Patient Representative).

Industry Representative (non-voting):

Theodore Reiss, M.D. was invited but unable to attend due to an urgent family matter.

Pulmonary-Allergy Drugs Advisory Committee Members Absent:

Peter E. Morris, M.D., William J. Calhoun, M.D

FDA Participants:

Robert Meyer, M.D., Badrul Chowdhury, M.D., Anne Trontell, M.D., M.P.H., Eugene J. Sullivan, M.D., FCCP, Sally Seymour, M.D., J. Harry Gunkel, M.D.

Open Public Hearing Speakers:

Chris Ward

Issue:

The committee discussed the implications of recently available data related to the safety of long acting beta-agonist bronchodilators.

The agenda proceeded as follows:

Call to Order and Opening Remarks

Erik R. Swenson, M.D.
Chair, Pulmonary-Allergy Drugs
Advisory Committee

Introduction of Committee

Conflict of Interest Statement

Mary Ann Killian
Program Integrity Advisor
Ethics and Integrity Staff
Office of Management Programs
Office of Management, FDA

FDA Introductory Remarks

Robert Meyer, M.D.
Director, Office of Drug Evaluation
II

Badrul Chowdhury, M.D.
Director, Division of Pulmonary-
Allergy Drug Products

Guest Speaker Presentation

An Overview of Long-Acting
Beta Agonists

Christine Sorkness, Pharm.D.
Professor of Pharmacy and
Medicine
University of Wisconsin

Sponsor Presentation

Opening Remarks

Glaxo Smith Kline
C. Elaine Jones, Ph.D.
Vice President, Regulatory Affairs

Salmeterol Review

Katharine Knobil, M.D.
Vice President,
Respiratory Clinical Development

Closing Remarks

C. Elaine Jones, Ph.D.
Vice President, Regulatory Affairs

Sponsor Presentation

Introduction

Novartis
Eric A. Floyd, M.S., M.B.A., Ph.D.
Vice President- Global Head RDI
Drug Regulatory Affairs
Novartis

Efficacy and Safety of Foradil®

Gregory P. Geba, M.D., M.P.H.
Vice President – U.S. Head RDI
Clinical Development and Medical
Affairs
Novartis

FDA Presentation

Salmeterol

Sally Seymour, M.D.
Medical Officer,
Division of Pulmonary-Allergy
Drugs

Formoterol

J. Harry Gunkel, M.D.
Medical Officer,
Division of Pulmonary-Allergy
Drugs

Open Public Hearing

Committee Discussion

1. The product labels of salmeterol containing products have been modified to include warnings related to the SMART study.

- a. Based on currently available information, what further actions, if any, do you recommend that the Agency take to communicate or otherwise manage the risks of severe asthma exacerbations seen in the SMART study?
 - Consider modifying the current Black Box Warning to either strongly discourage monotherapy with salmeterol or strongly encourage co-administration with an inhaled corticosteroid.
 - Include language that emphasizes that this product may not work equally in all patients. Particularly, in patients of various ethnicities, genotypes, and phenotypes as well as in patients labeled “Brittle Asthmatics” and that salmeterol may even have negative outcomes in some of these patients with or without inhaled corticosteroids.
 - Simplify the package insert so that the important information is easily located and evaluated (i.e. providing information about relative risk in figures or tables rather than just in direct text).
 - Re-examine the method in which information is disseminated to both healthcare providers and patients. (Dear Doctor letters may not be the best method).
 - Provide medication guides and direct patient information that is in a form understandable to the patient.
 - The package insert and the patient information should emphasize adherence to the prescribed dosing regimen.
 - Patient information should address drivers of exacerbations and provide clear information about early intervention with fast acting bronchodilators when acute symptoms arise. Patients should be given information on how to minimize or reduce acute exacerbations.
 - The language in the patient insert should avoid the terminology “rescue inhaler” as patients sometimes misinterpret the meaning and could result in delayed use of fast-acting bronchodilators.
 - The Black Box Warning should be maintained on all salmeterol containing products (i.e. Serevent and Advair).

b. Based on the currently available information, do you agree that salmeterol should continue to be marketed in the United States?

YES = 13

NO = 0

Abstain = 0
Total = 13

2. The label of the formoterol containing product does not include warnings comparable to the warnings that are present in the salmeterol containing products.

- a. Based on the currently available information, should the label of the formoterol containing product include warnings similar to those in the salmeterol label?
YES = 12
NO = 0
Abstain = 1
Total = 13

As a caveat to the votes of yes, many members suggested that the label include language to the effect: Another drug in this class of medications has demonstrated a signal for negative outcomes in selected populations (African Americans, specific genotypes and phenotypes). Data is insufficient to determine if this also applies to formoterol, however it is possible that the signal is indicative of a class effect.

- b. Based on the currently available information, do you agree that formoterol should continue to be marketed in the United States?
YES = 13
NO = 0
Abstain = 0
Total = 13

3. What further investigation, if any, do you recommend to be performed by GSK that can improve the understanding of the nature and magnitude of the risk of salmeterol?

- Some studies are already in process (i.e. Medicaid Study) which can answer some of the questions raised about salmeterol. Timely reporting of the results is strongly encouraged.
- Studies that evaluate the effects of age, gender, ethnicity, genetics and phenotypes on the safety of this drug should be undertaken.
- A suggestion to also utilize systems databases akin to the Medicaid database to obtain information (i.e. the VA hospital database) was made.
- A suggestion was made that both GSK and Novartis partner in their efforts to obtain the necessary information.
- A case control hospital surveillance study of fatal and near-fatal asthma episodes that uses linked pharmacy databases and also captures phenotype and genotype information.
- A Translational Research Project of subsets who are non-responders to salmeterol. Find out why they don't respond. Is it because of genetics or acquired traits?
- Ideally, it would have been better to take the SMART study to the pre-specified end points, but since that did not happen, a study to assess the impact of phenotypes, genotypes, and environmental factors (i.e. tobacco and occupational exposures). These variables pose complex interactions and can be confounding factors.
- An effort should be made to find out the phenotypes of "Brittle Asthmatics" at the time of death.

- A study to determine how much medicine is needed in specific patient populations (i.e. pediatric patients where a high dose to Body surface area ratio may increase risks). Also evaluate how environmental factors and level of patient education impacts this.
 - Current Translational studies may not be enough to answer real world therapy questions. The committee would like data on how many patients are on combination therapy (LABA and inhaled corticosteroid) vs. inhaled corticosteroids alone. Address salmeterol monotherapy. What percent of patients are using monotherapy vs. combination therapy?
4. What further investigation, if any, do you recommend to be performed by Novartis that can improve the understanding of the nature and magnitude of the risk of formoterol?
- A clinical trial to compare both drugs (salmeterol and formoterol) head to head for severe asthma and asthma related deaths.
 - Many members suggested that all the same requests made of GSK should apply to Novartis.
 - A trial similar to the SMART study for formoterol that focuses on the target populations (African Americans, specific phenotypes and genotypes) powered to determine if the negative outcomes are in fact a class effect.
 - Pediatric dosing studies are needed.

4:45 p.m. Adjourn