These summary minutes for the February 9 and 10, 2006, meeting of the Drug Safety and Risk Management Advisory Committee were approved on ___2/22/06____.

I certify that I attended the February 9 and 10, 2006, meeting of the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____//S//_____
Victoria Ferretti-Aceto, Pharm.D.
Executive Secretary

_____//S//_____
Peter Gross, M.D.
Chair

Drug Safety and Risk Management Advisory Committee
February 9, 2006

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#
Slides shown at the meeting will be available at least 3 business days after the meeting at the same website.

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

The Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 9, 2006, at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Peter Gross, M.D. chaired the meeting. There were approximately 200 in attendance.

Drug Safety and Risk Management Advisory Committee Members (voting):
Peter Gross, M.D. (Chair), Stephanie Crawford, Ph.D., M.P.H., Terry Davis, Ph.D., Jacqueline Gardner, Ph.D., M.P.H., Eleanor Gomez-Fein, Pharm.D., Arthur Levin, M.P.H.[CR], Henri Manasse, Jr., Ph.D., Robyn Shapiro, J.D.

Drug Safety and Risk Management Advisory Committee Members (absent):
Michael Cohen, M.S., D.Sc., Eric Holmboe, M.D., Louis Morris, Ph.D., Richard Platt, M.D., M.Sc.

Drug Safety and Risk Management Advisory Committee Members (non-voting):
Annette Stemhagen, Dr. P.H. (Industry Representative)

Consultants/Special Government Employees (voting):
Ralph D'Agostino, Ph.D., Deborah Dokken, M.P.A. [PR], Thomas Fleming, Ph.D., Curt Furberg, M.D., Ph.D., Sean Hennessy, Pharm.D., Ph.D., John Moore, M.D., M.P.H., Steven Nissen, M.D., Marsha Rappley, M.D.

Consultants/Special Government Employee/Guest Speaker (non-voting)
Elizabeth Andrews, M.P.H., Ph.D.

FDA Speakers:
Gerald DalPan, M.D., M.H.S., Andrew Mosholder, M.D., M.P.H., Kate Gelperin, M.D., M.P.H., David Graham, M.D., M.P.H.

FDA Participants:
Gerald DalPan, M.D., M.H.S., Solomon Iyasu, M.D., Tom Laughren, M.D., Andrew Mosholder, M.D., M.P.H.

Open Public Hearing Speakers:
- Georgia Gross, Self-Interest
- Clinton Libbey, AbleChild
- Ellen Bleecker Liversidge, Alliance for Human Research Protection
- Sue Parry, International Center for the Study of Psychiatry and Psychology (ICSPP)

Open Public Hearing Speakers cont'd:

- M. Christopher Griffith, M.D., Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD)
- Sandra Lucas, Citizen Commission on Human Rights
- Lawrence Greenhill, M.D., American Academy of Child and Adolescent Psychiatry (AACAP) and American Psychiatric Association (APA)
- Allen Jones, Alliance for Human Research Protection
- Todd Gruber, M.D., M.P.H., Novartis Pharmaceuticals
- Albert Allen, M.D., Ph.D., Eli Lilly and Company

On February 9, 2006, the committee considered approaches that could be used to study whether drugs used for the treatment of attention deficit hyperactivity disorder increase the risk of cardiovascular outcomes in children and adults.

Peter Gross, M.D. (Committee Chair), called the meeting to order at 8:00 a.m. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Victoria Ferretti-Aceto, Pharm.D. The agenda proceeded as follows:

Call to Order and Introductions	Peter Gross, M.D., Chair Drug Safety and Risk Management Advisory Committee (DSaRM)
Conflict of Interest Statement	Victoria Ferretti-Aceto, Pharm.D. Executive Secretary, DSaRM
Opening Remarks	Dr. Gerald Dal Pan, M.D., M.H.S., Director, Office of Drug Safety
Overview of Attention Deficit Hyperactivity Disorder (ADHD) and its Pharmacotherapy	Andrew Mosholder, M.D., M.P.H.
Studying Cardiovascular Risk with Drug Treatments of ADHD	Kate Gelperin, M.D., M.P.H.
ADHD Drugs and Cardiovascular Outcomes: Feasibility Study Results	David Graham, M.D., M.P.H.
Challenges of Studying Cardiovascular Outcomes in ADHD	Elizabeth Andrews, M.P.H., Ph.D.
Open Public Hearing Statement	
Introduction of Questions	Gerald Dal Pan, M.D., M.H.S.

Prior to the questions proposed by the Agency, the Committee agreed to take a vote on the following issues:

1. Whether to recommend the distribution of Med Guides to warn of potential cardiovascular risks with the stimulant class of drugs used for the treatment of ADHD.

The Committee voted:
15 YES
0 NO
1 ABSTAIN

in favor of requiring distribution of Med Guides with the stimulant class of ADHD drugs

2. Whether to recommend a black box warning of the cardiovascular risks with the stimulant class of drugs used for the treatment of ADHD.

The Committee voted:
8 YES
7 NO
1 ABSTAIN

in favor of requiring the black box warning be added to alert users of the cardiovascular risks of the stimulant class of drugs for the treatment of ADHD. Those that voted NO expressed concern over the need for a broader and more effective communication to patients of risk and the potential of these drugs to harm.

Question to the Committee:

The discussion presented today illustrates the challenges of post-marketing drug safety assessments. While FDA has received case reports of cardiovascular adverse events in patients taking medications for ADHD, these reports by themselves do not establish a causal relationship. We are asking the committee to consider the feasibility of various epidemiologic and other approaches to investigate and characterize this safety signal and to address specific methodological considerations.

Questions:

Based on today's presentations and discussion:

1. Please identify and discuss the most important outcomes to study in both children and adults. In your discussion, please consider
    - whether the choice of outcomes differs by age group?
    - validation of outcomes?
    - selection of a comparison group?

Discussion

The choice of outcomes discussed by the Committee for both pediatric and adult populations included sudden death, myocardial infarction, stroke, cardiovascular death, and overall mortality.

Suggestions by the Committee for selection of comparison groups included children with the disease, but not taking the drug (unexposed person time) and the general population of non-diseased children (to determine background).

Please see transcript for detailed discussion.

2. Please comment on whether ADHD drugs should be studied individually or collectively.

Discussion

Comments from the Committee included:

- *All of the amphetamine-like drugs should be considered the same until proven otherwise.*
- *These drugs should be looked at individually and then class inferences should be made, as opposed to looking at the class as a whole.*
- *Short term studies of ambulatory blood pressure and heart rate should be conducted to understand the physiological differences and similarities.*
- *Adverse drug reactions databases could be used to observe how fine the differences are (regarding blood pressure and heart rate changes) compared to other stimulants, not just placebo.*

Please see transcript for detailed discussion.

3. Which of the following approaches seems best to study cardiovascular outcomes with ADHD drugs? Please consider methodological issues, the nature of the outcomes, time needed to conduct the study, and cost issues in the following:

    - Prospective case-control study
    - Large simple trial
    - Case-control or cohort study within a claims database
    - Other approaches

Please see transcript for detailed discussion.

4. What are the important confounders relating to use of ADHD drugs in both children and adults that should be considered in a study of ADHD drugs and cardiovascular outcomes?

Discussion

The Committee noted that in adults, important confounders would include those factors that increase cardiovascular risk (age, gender, high blood pressure, high cholesterol, smoking, diabestes). In children, the most important confounders would include pre-existing cardiovascular structural abnormalities. Other confounders mentioned include genetic predisposition, comorbid conditions, other medication use and abuse (especially those drugs associated with changes in cognition and behavior) and medication adherence.

Please see transcript for detailed discussion.

5. Please discuss study approaches that may explore duration of use of ADHD drugs. Specifically, consider whether there are feasible study methods that could be undertaken to characterize longer term cardiovascular risk (in any age group) with chronic ADHD drug therapy.

Discussion

The Committee suggested studying ventricular function over time, as seen by ejection fraction (observed decrease in ejection fraction over time), and matching patients with long term use of ADHD drugs to case controls. Issues brought up by the Committee included asking whether the risks emerge early on? do they stop once drug use has discontinued? do different durations of drug use increase the risk? It was suggested that randomized trials could be used to determine at what point risk occurs.

Please see transcript for detailed discussion.

The meeting adjourned at approximately 4:45 PM.

Drug Safety and Risk Management Advisory Committee
February 10, 2006

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#
Slides shown at the meeting will be available at least 3 business days after the meeting at the same website.

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

The Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 10, 2006, at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Peter Gross, M.D. chaired the meeting. There were approximately 100 in attendance.

Drug Safety and Risk Management Advisory Committee (voting):
Peter Gross, M.D. (Chair), Stephanie Crawford, Ph.D., M.P.H., Terry Davis, Ph.D., Jacqueline Gardner, Ph.D., M.P.H., Eleanor Gomez-Fein, Pharm.D., Arthur Levin, M.P.H.[CR], Henri Manasse, Jr., Ph.D., Robyn Shapiro, J.D.

Drug Safety and Risk Management Advisory Committee (absent):
Michael Cohen, M.S., D.Sc., Eric Holmboe, M.D., Louis Morris, Ph.D., Richard Platt, M.D., M.Sc.

Drug Safety and Risk Management Advisory Committee Members (non-voting):
Annette Stemhagen, Dr. P.H. (Industry Representative) [recused from isotretinoin portion]

Consultants (voting):
Curt Furberg, M.D., Ph.D., Sean Hennessy, Pharm.D., Ph.D.

FDA Speakers:
Gerald DalPan, M.D., M.H.S., Andrew Mosholder, M.D., M.P.H., Kate Gelperin, M.D., M.P.H., David Graham, M.D., M.P.H.

FDA Participants:
Gerald DalPan, M.D., M.H.S., Susan Cummins, M.D., M.P.H., Sharon Hertz, M.D., Jill Lindstrom, M.D., F.A.A.D.

Open Public Hearing Speakers:

- Tim Cochran, Healthcare Distribution Management Association
- Diane Thiboutot, M.D., American Academy of Dermatology Associations

---

On February 10, 2006, the committee was briefed on developments in the Office of Drug Safety and received updates on the Drug Safety Oversight Board and Agency actions for the COX-2 selective Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and the risk management program for the isotretinoin products.

Peter Gross, M.D. (Committee Chair), called the meeting to order at 8:00 a.m. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Victoria Ferretti-Aceto, Pharm.D. The agenda proceeded as follows:

Call to Order and Introductions	Peter Gross, M.D., Chair Drug Safety and Risk Management Advisory Committee (DSaRM)
Conflict of Interest Statement	Victoria Ferretti-Aceto, Pharm.D. Executive Secretary, DSaRM
Open Public Hearing Statement	
Office of Drug Safety Updates	Gerald Dal Pan, M.D., M.H.S., Director, Office of Drug Safety
New Drug Safety Initiatives and the Drug Safety Oversight Board	Susan Cummins, M.D., M.P.H.
An Update on NSAID Labeling and Data Review	Sharon Hertz, M.D.
Introduction to Isotretinoin Risk Management Program	Jill Lindstrom, M.D., F.A.A.D.
iPLEDGE Isotretinoin Pregnancy Risk Management Program	Susan Ackermann Shiff, PhD Global Head, Risk Management, Hoffmann-La Roche Inc. Christine Mundkur Senior VP, Quality and Regulatory Counsel, Barr Laboratories, Inc. James Shamp Director, Covance, Inc.

The committee adjourned at approximately 12:45 PM.