Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland

Summary Minutes of the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on July 30, 2007.

On July 30, 2007 the committee discussed Cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

These summary minutes for the July 30, 2007 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on Tuesday, August 1, 2007.

I certify that I attended the July 30, 2007 joint meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Miller, M.P.H., R.N.	Date	Clifford J. Rosen, M .D.	Date
Designated Federal Official		(Acting) Chair	

A verbatim transcript will be available in approximately 4-6 weeks from the date of the meeting, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic

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

The Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 30, 2008 at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and the sponsor (GlaxoSmithKline). The meeting was called to order by Clifford J. Rosen, M.D (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 450 persons in attendance. There were 16 speakers for the Open Public Hearing session.

Issue: Cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Kenneth D. Burman; M.D.; Jessica W. Henderson, Ph.D.; Katherine M. Flegal, Ph.D.; Clifford J. Rosen, M.D.;

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Sean Hennessy, Pharm.D, Ph.D.; Judith M. Kramer, M.D., M.S.; Timothy S. Lesar, Pharm.D.;

Special Government Employee Consultants (Voting): Ruth S. Day, Ph.D.; Judith Fradkin, M.D.; Nancy L. Geller, Ph.D.; Allison Goldfine, M.D.; Eric S. Holmboe, M.D., F.A.C.P.; Rebecca Killion (Patient Representative); Arthur A. Levin, M.P.H.; Arthur J. Moss, M.D. [participating via teleconference]; Lewis S. Nelson, M.D., F.A.C.E.P.; David Oakes, PhD. [participating via teleconference]; Thomas G. Pickering, M.D., D.Phil.; Peter J. Savage, M.D.; David S. Schade, M.D.; Morris Schambelan, M.D.; John R. Teerlink, M.D.; Gerald van Belle, Ph.D.

Special Government Employee Consultants (Non-Voting): Curt D. Furberg, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-Voting):
Steven W. Ryder, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Non-Voting):
Annette Stemhagen, Dr.Ph. (Industry Representative)

Guest Speakers (Non-Voting): David Gordon, M.D., Ph.D., M.P.H.; Robert E. Ratner, M.D.

Consultants (Non-Voting): Steven Nissen, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present: Nelson B. Watts, M.D. (Chair); Sonia Caprio, M.D.; Michael A. Proschan, Ph.D.

Drug Safety and Risk Management Advisory Committee Members Not Present: Richard Platt, M.D., M.Sc.; Terry C. Davis, Ph.D.; Susan R. Heckbert, M.D., Ph.D.

FDA Participants (Non-Voting): Douglas C. Throckmorton, M.D.; Sandra L. Kweder, M.D.; Robert J. Meyer, M.D.; Mary H. Parks, M.D.; Gerald Dal Pan, M.D., M.H.S.; Mark I. Avigan, M.D., C.M.; Robert T. O'Neill, Ph.D.

Designated Federal Official: Cathy A. Miller, M.P.H., R.N.

Open Public Hearing Speakers:
Sidney M. Wolfe, M.D., Director, Public Citizen's Health Research Group; J. Rick Turner, Ph.D., P.G.C.E., Campbell University School of Pharmacy; George A. Diamond, M.D., F.A.C.C.; Sanjay Kaul, M.D., F.A.C.C., Cedar-Sinai Medical Center Division of Cardiology; Richard Hellman, M.D., F.A.C.P., F.A.C.E., President, American Association of Clinical Endocrinologists; Jerome V. Tolbert, M.D., Ph.D.; Eileen Rivera Ley, Director, Diabetes Initiatives, Diabetes Action Network, National Federation of the Blind; Gail Brashers-Krug, Voice of Diabetic and Diabetes Action Network; Bruce Trippe, M.D., F.A.C.E., Endocrinology Associates of Montgomery; Raul Fernandes; Richard E. Ralston, Executive Director, Americans for Free Choice Medicine; Cahrles E. Steele; Farhad Zangeneh, M.D., F.A.C.P., F.A.C.E., Endocrine, Diabetes and Osteoporosis (EDOC); Jamie Davidson, M.D., Endocrinologist; Michael R. Peterson, D.V.M., M.P.H./Thomas Bacon, Pharm.D.

The agenda was as follows:

Call to Order and Introductions	**Clifford J. Rosen, M.D.** (Acting) Committee Chair
Conflict of Interest Statement	**LCDR Cathy A. Miller, M.P.H.** Designated Federal Official Endocrinologic and Metabolic Drugs Advisory Committee
Introduction/Background	**Mary H. Parks, M.D.** Director, Division of Metabolism and Endocrine Products, CDER, FDA

PRESENTATIONS:

Guest Speaker Presentation:

Achieving Diabetes Targets: Where Are We and How Can We Do Better?	**Robert E. Ratner, M.D.** Vice-President of Scientific Affairs MedStar Research Institute Washington, DC

GlaxoSmithKline Presentations:

. Introduction	**Ronald L. Krall, M.D.** Senior Vice President and Medical Officer GlaxoSmithKline
Review of Data	**Murray W. Stewart, D.M., FRCP** Vice President, Clinical Development GlaxoSmithKline
Conclusions	**Ronald L. Krall, M.D.**
	Clarifying Questions from the Committee
	Break

FDA Presentations:

FDA Meta-Analysis	**Joy D. Mele, M.S**. Statistician, FDA/CDER Office of Biostatistics, Division of Biometrics II
Overview of Large, Long-Term,	**Karen M. Mahoney, M.D.**

Prospective Trials of Thiazolidinediones	Medical Officer, FDA/CDER Division of Metabolism Endocrine Products

NIH Speaker Presentation:

Use of Rosiglitazone in the BARI 2D Trial	**David J. Gordon, M.D., Ph.D.** Division of Cardiovascular Diseases National Institute of Health (NIH) National Heart, Lung and Blood Institute

FDA Presentations (Continued):

Observational Studies: Effect of Anti-Diabetic Agent Choice on Cardiovascular Morbidity and Mortality in Type II Diabetes Mellitus	**Kate Gelperin, M.D., M.P.H.** Medical Officer, FDA/CDER Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation
Assessment of health risks and Benefits associated with rosiglitazone	**David Graham, M.D., M.P.H.** Associate Director, FDA/CDER Associate Director for Science and Medicine, Office Surveillance and Epidemiology
Conclusions and Summary	**Robert Meyer, M.D.** Director, FDA/CDER Office of New Drug Evaluation II **Gerald Dal Pan, M.D., M.H.S.** Director, FDA/CDER Office of Surveillance and Epidemiology
	Lunch
	Open Public Hearing
.	**Questions to the FDA/Discussion**
	Break
`	**Questions to the Committee**
	Adjourn

Questions to the Committee:

1. Please comment on the contribution of the meta-analysis of the 42 controlled clinical trials (e.g., strengths and limitations) to the understanding of cardiac ischemic risk for Avandia.

- ***Most of the committee members agreed that there was at least a strong signal for increased cardiac ischemic risk, though concerns were raised about the short duration of the trials; the quality of the data; low number of cardiac events; lack of cardiac eventadjudication; and concerns about the heterogeneity of the study population.***
- ***The committee further identified subpopulations at potential risk, such as nitrate users, those with established cardiovascular disease and those with coexistent insulin therapy, who appeared to have an increased risk.***
- ***The committee pointed out that the outcome of interest in these trials, at the time they were designed and conducted, was not ischemic cardiac events, making the study data difficult to***

interpret, though they raise awareness of a strong signal; adverse events in the 42 trials were not collected in a standardized, prespecified or adjudicated in an ongoing way

- ***The committee requested that the FDA have more rigorous requirements for clinical trials to assure the follow-up of subjects who withdraw from assigned treatment, even for trials based on short-term data, with reporting of all adverse events.***

(See transcript for detailed discussion)

2. Please comment on the contribution of the observational cohort studies (e.g., strengths and limitations) to the understanding of cardiac ischemic risk for Avandia.

- ***There was considerable discussion from the committee on the observational studies and their potential value. Some on the committee stated that the observational studies are helpful in capturing what is actually happening in practice and getting a sense of population risk.***
- ***While some of the committee members commented that the observational studies were high quality and carefully done, they also raised concerns about biases, difficulty interpreting the data for users [treated] versus non-users [not-treated].***
- ***The committee cautioned that observational studies have in the past, yielded conflicting results from those of randomized clinical trials (e.g. hormone replacement therapy), therefore there is limited weight we can place on these studies***
- ***The committee emphasized the importance that we are not comparing this drug to placebo since diabetics need to take something to control their disease***
- ***The committee commented that the data may suggest that the difference between the two TZDs [rosiglitazone and pioglitazone] may not be as great as claims that have been made based on information obtained from the observational studies***
- ***Some of the committee suggested that if the randomized controlled trials will not give us the answers we need, we are left with information that can be obtained from well designed observational studies, along with a registries approach, to capture out of hospital events***

(See transcript for detailed discussion)

3. Please comment on the contribution of large randomized controlled trials of rosiglitazone (e.g., strengths and limitations of DREAM, ADOPT, and RECORD) to the understanding of cardiac ischemic risk for Avandia.

- ***The committee commented that given the real world setting for treatment of diabetes is no longer no treatment versus drug, caution should be taken about discarding studies with a very practical clinical design like RECORD, given the hard adjudicated endpoint; however, there are concerns about DREAM and ADOPT, given the inclusion of non-diabetic or new diabetic patients in the studies; the risk in these two studies is very different***
- ***The committee expressed concern and disappointment that these studies will have the 'power' to negate whether there is potentially a significant increase in risk. The committee also expressed its concern that these trials do not study the patients of interest, and in fact, excluded the patients that we are concerned about; therefore lack of a signal for the outcomes in these trials may not necessarily inform decisions regarding risk for Avandia..***
- ***Though there is evidence of increased CVD risks with Avandia, the committee identified the need for more long-term data and within sub-groups, particularly patients taking insulin+rosiglitazone; patients with congestive heart failure and those taking nitrates; and the elderly population.***

- ***The committee commented that the FDA is in a position to make a greater demand, in terms of accumulating more endpoints, specifically in RECORD, and even expanding the number of patients.***
- ***The committee added that, while there is value in all the varied types of studies [meta-analysis, observational studies and long-term trials], there needs to be a model to evaluate the conclusions of all of these studies.***
- ***The committee members expressed an interest in additional analyses that would evaluate all relevant cardiovascular endpoints occurring to a subject in the trial, and not limiting analyses simply to the 'time to first event', especially for longer term clinical studies of several years duration.***

(See transcript for detailed discussion)

4. Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus **(VOTE requested)?**
    - If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes mellitus?

YES: 20 NO: 3

- ***Many of the committee members expressed their reluctance to draw conclusions comparing risk level of Avandia versus other available therapies, until additional data has been reviewed (e.g. Takeda study of pioglitazone)***
- ***Some of the committee voting 'YES' qualified their vote by adding that current data could be categorized as 'suggestive of' rather than 'evidence of' an increased cardiac ischemic risk with Avandia.***
- ***Many of the committee members qualified their 'YES' answer to the question of greater risk with Avandia, by identifying subgroups at increased risk, noting the limitations of comparison to placebo, and noting the increased risk in patients taking insulin. The committee added the need to emphasize the risks of other therapies such as sulfonylureas. The committee further commented on its concern about the lack of a dose-response relationship exhibited in the studies.***

(See transcript for detailed discussion)

5. Does the overall risk-benefit profile of Avandia support its continued marketing in the US **(VOTE requested)?**
    - If yes, please comment on what FDA should do to maximize the risk-benefit considerations (e.g., limit to certain patients, incorporate a boxed warning….)

YES: 22 NO: 1

- ***Some of the committee felt that the removal of Avandia from the market would be a draconian measure based on the current information available, emphazing the necessity of having a TZD drug available, as an option to treat diabetes***
- ***Most of the committee provided recommendations for labeling changes regarding ischemic risks. Recommendations included a black box warning for use in patients with heart failure;***

a contraindication for use with insulin though a few of the committee participants suggested a removal of the indication rather than contraindication; a warning about the use with anti-anginals (e.g. ARBs); monitoring and patient education; and perhaps a statement about ongoing research in progress. A few of the committee members suggested a black box warning for all severe congestive heart failure, concomitant insulin use, and severe arterioscleratic heart disease and use of nitrates

- ***A few committee participants expressed caution in recommending labeling changes for contraindications in certain subgroups and would also not recommend black box warning but would add warning regarding cardiovascular risks to the text of labeling.***
- ***Concerns were also raised that there is not enough emphasis on addressing the risk management issues, specifically as underrepresented in the sponsor's Risk Management Plan identified in the background for this meeting. Committee comments regarding maximizing risk-benefit considerations include those mentioned in earlier discussion such as patient registries, a reevaluation of the sponsor Risk Management Plan, and more comprehensive clinician education, citing past observations identified after the distribution of "Dear Healthcare Professional" letters.***

The committee adjourned at approximately 5:45 p.m.

(See transcript for detailed discussion)