Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE #64

September 26, 1996
Bethesda Holiday Inn
8120 Wisconsin Avenue, Bethesda MD

Members Present
Henry G. Bone, III, M.D., Chair
Robert Marcus, M.D.
Robert A. Kreisberg, M.D.
Colleen A. Colley, Pharm.D.
Mark Molitch, M.D.
Maria I. New, M.D.
Robert Sherwin, M.D.
Cathy Critchlow, Ph.D.
D. Roger Illingworth, M.D., Ph.D.

Consultants
Joanna Zawadzki, M.D.
John M. Flack, M.D., M.P.H.

Members Absent
Jules Hirsch, M.D.
Jose Francisco Cara, M.D.

FDA Participants
James M. Bilstad, M.D.
Solomon Sobel, M.D.
Eric Colman, M.D.
Gloria Troendle, M.D.
Bruce Stadel, M.D., M.P.H.

Guest Experts

Executive Secretary
Kathleen R. Reedy

These summary minutes for the September 26, 1996 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on 3/28/00.

I certify that I attended the September 26, 1996 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy
Kathleen R. Reedy,
Executive Secretary

Henry G. Bone III, M.D.
Chairperson

Meeting #64 of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration Center for Drug Evaluation and Research met at the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD on September 26, 1996 to consider NDA 20-632; Meridia™, sibutramine hydrochloride monohydrate presented by Knoll Pharmaceutical Company. It was attended by approximately 200 people. The Committee members had been provided a briefing document from the sponsor and the agency approximately nineteen days before the meeting.

The OPEN SESSION began at 8:00 with the call to order, introductions of Committee members and opening comments by Henry G. Bone III, M.D., Chair. The meeting statement was read by Kathleen Reedy, Executive Secretary of the Endocrinologic and Metabolic Drugs Advisory Committee.

Speakers at the Open Public Hearing were:

1. Richard Atkinson, M.D., President,
   American Obesity Association
   Professor of Medicine and Nutritional Sciences
   Director of Beers-Murphy Clinical Nutrition Center
   University of Wisconsin
2. John Foreyt, Ph.D.
   Director of Nutritional Research Clinic
   Professor, Department of Medicine
   Baylor College of Medicine
3. Kris Ernst, American Society of Diabetes Educators
4. Barbara Hanson, Ph.D., past Presedent
   American Society of Clinical Nutrition
5. Valerie Rochester, National Council Negro Women
6. Lynn McAfee, Council on Size and Weight Discrimination

All speakers supported availability of medication as part of an armamentarium of treatments for obesity. In addition, similar opinions were expressed in letters submitted from:

1. American Heart Association
   Jennifer Johnson, Office of Public Advocacy
2. American Diabetes Association, National Center
   Alan Altschuler, Chair of the Board
   Philip E. Cryer, MD, President
   Belinda P. Childs, MN, RN, CDE, President, Health Care & Education
3. Marion J. Franz, MS, RD, CDE
   International Diabetes Center
4. Denise E. Bruner, MD, bariatric practioner
5. North American Association for the Study of Obesity
   Robert H. Eckel, M.D., President

The Knoll Pharmaceutical Company presentation for Meridia™, NDA 20-632; sibutramine hydrochloride monohydrate, consisted of:
Introduction: Mel Spigelman, M.D.
Obesity Overview: F. Xavier Pi-Sunyer, M.D.
Pre-Clinical: David Heal, M.D.
Pharmacokinetics/Efficacy: Carl Mendel, M.D.
Safety: Timothy Seaton, M.D.
Epidemiologic Benefit/Risk: Sylvia Smoller, Ph.D.
Clinical Benefit/Risk: Michael Lean, M.D.
Phase IV/Conclusion: Mel Spigelman, M.D.

The FDA Presentation consisted of:
Medical: Eric Colman, M.D., Medical Officer,
Division of Metabolic and Endocrine Drug Products
Epidemiology: Bruce V. Stadel, M.D., M.P.H.
Division of Metabolic and Endocrine Drug Products
Hypertension: John M. Flack, M.D., M.P.H.,
Medical Director, Hypertension Center
Bowman Gray School of Medicine, Wake Forest University

The Commmittee discussed the presentations, the issues raised and considered the following questions:

1. Does sibutramine meet the Guidance Criteria of effectiveness for weight loss?
YES - 9 NO - 0

2. Is the pressor effect of sibutramine clinically important?
YES - 8 NO - 0 ABSTAIN - 1

3. Do the benefits of sibutramine outweigh the risks?
YES - 4 NO - 5

4. If sibutramine were to be approved for marketing, should there be a Phase 4 study?
YES - 9 NO - 0

Recommendations for a phase 4 study include:
placebo control studies (unanimous)
studies that include ethnic diversity in subjects
studies that include older people
studies that include subjects with comorbid conditions
data on studies with diabetes, hyperlipidemia, hypertension
compliance of subjects with diet and dosing regimens
data on off label use
small studies of small scope in subgroups, particularly diverse hypertensive groups and lower dosage trials

Summary:
This drug was determined to be efficacious according to the draft guidance document for weight loss drugs, on a responder basis and on a mean effect basis at the higher doses proposed. The Company forthrightly acknowledged that the drug causes systolic and diastolic increases in blood pressure and was expected to have an effect on morbidity and mortality to offset the hypertensive effects. Discussion revolved around relative ratio of risk to benefit. As forseen in the draft guidance document, the evaluation of effects on comorbid conditions was an important consideration in risk/benefit analysis. The limited and inconsistent benefits of the drug on lipid metabolism and diabetic patients were of concern to the Committee; limited the confidence that beneficial effects would offset risks. The Committee expressed unanimous support for phase 4 studies if the drug is approved as essential and placebo control necessary to add data to the currently deficient pool regarding comorbid conditions.

The meeting was adjourned at 3:30 pm.

Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee