Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

July 26, 2001
Bethesda Holiday Inn
8120 Wisconsin Avenue, Bethesda, MD

Members Present
Allan Sampson, Ph.D.
Deborah Grady, M.D., M.P.H.
Marie Gelato, M.D., Ph.D.
William Tamborlane, M.D.
Lynne Levitsky, M.D.

Consultants
Robert Kreisberg, M.D.
Jose Cara, M.D.
Wendy McBrair, R.N., M.S., C.H.E.S
Rebecca Killion

Members Absent
Thomas Aoki, M.D.
Barbara Lukert, M.D.
Janet Silverstein, M.D.
Glenn Braunstein, M.D.

Executive Secretary
Kathleen R. Reedy, RDH, MS

FDA Participants
Robert I. Misbin, M.D.
Dragos G. Roman, M.D.
Saul Malozowski, M.D., Ph.D., M.P.H.
David G. Orloff, M.D.
John Jenkins, M.D.

Guest Experts

These summary minutes for the July 26, 2001 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on September 21, 2001

I certify that I attended the July 26, 2001 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy,
Executive Secretary

Robert Kriesberg, M.D.
Chairperson

The 76th Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was held on July 26 and 27, 2001 at the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Versailles Rooms I, II and III.

On July 26, 2001 the meeting was called to Order at 8 am by Robert A. Kreisberg, M.D., Acting Chair to consider **NDA 21-332, Symlin ™ (pramlintide acetate) Amylin Pharmaceuticals, Inc.** There were approximately 150 people in the audience. The committee had been provided with a briefing document from the sponsor and the FDA four weeks before the meeting.

Following the reading of the Meeting Statement by Kathleen Reedy, Executive Secretary, David G. Orloff, M.D., Director of the Division of Metabolic and Endocrine Drug Products extended a welcome and introduction to the topic for the day.

The Amylin Pharmaceuticals, Inc. Presentation was as follows:
Overview: Joann L. Data, MD,PhD, Sr.VP Regulatory Affairs and Quality Assurance
Unmet Medical Need: Kenneth Polonsky, MD, Adolphus Busch Professor of Medicine and Chairman, Department of Medicine, Washington University School of Medicine
Pharmacology of Pramlintide: Andrew Young, MD, PhD, VP, Research at Amylin
Clinical Program for Pramlintide: Orville Kolterman, MD, Sr. VP Clinical Affairs, Amylin
Risk/Benefit/Summary: Alain Baron, VP Clinical Research at Amylin

The FDA Presentation consisted of:
Efficacy: Robert I. Misbin, M.D., Medical Officer
Safety: Dragos G. Roman, M.D., Medical Officer
Division of Metabolic and Endocrine Drug Products.

Speakers at the Open Public Hearing were:
1. Claresa Levitan, M.D., Washington, DC
2. Anna M. Wuertenberg, patient, Washington, DC
3. Susan Joy Benesh, patient, Odenton, MD
4. Rosalie Ashcraft, patient
5. Chris Brown, patient, Chicago, IL
6. Laura L. Want, RN, MS, CDE, CCRC, Washington, DC
7. Sidney M. Wolfe, M.D., Director, Public Citizen Health Research Group
8. John Pullman, M.D., Butte, MT
9. Davida Kruger, R. N., C. N. S. , Detroit, MI

Alvin J. Lorman, Washington, DC, submitted written information.

Following the Charge to the Committee by David G. Orloff, M.D. the participants engaged in discussion and addressed the following questions posed by the agency.

EFFICACY

1. Based on the information presented by the sponsor in the NDA, are the data adequate to establish the efficacy of pramlintide in combination with insulin for the treatment of patients with
   a. Type 1 DM? **Yes – 8** **No - 1**
   b. Type 2 DM? **Yes – 8** **No - 1**

   If the answer to either of the above is no, what additional data would be required?
   Higher Ns in type 2 trials and arms with insulin and metformin combination.
   Track and document fluctuations/excursions of glycemia

2. Based on the information presented by the sponsor in the NDA, were the study designs adequate to guide physicians in the effective use of pramlintide in combination with insulin in
   a. Type 1 DM? **Yes – 0** **No - 9**
   b. Type 2 DM? **Yes – 3** **No - 6**

   Consider with regard to
   i. identification of effective dose(s) of pramlintide
   ii. adjustments of the insulin regimen to achieve optimum glycemic control
   iii. use of pramlintide under conditions of strict glycemic control (i.e., to meet or exceed ADA goals)

   If the answer to either of the above is no, what additional data would be required?
   Broader study, multiple arms, dosing regimens with flexible insulin guide,
   Large trial of Sponsor proposed 30 mg dose with 10-20% reduction in insulin.
   Intense monitoring in initial 4/wk studies to detect hypoglycemia.
   Type 2 meals and exercise components as well as quality of life.

SAFETY

3. Based on the information presented by the sponsor in the NDA, are the data adequate to define the safety profile of pramlintide when used in combination with insulin in
   a. Type 1 DM? **Yes – 1** **No - 8**
   b. Type 2 DM? **Yes – 2** **No - 7**

   If the answer to either of the above is no, what additional data would be required?
   Type 1: for initiation therapy; analysis, follow up of nausea and hypoglycemia
   Type 2: larger study and efficacy

4. Based on the information provided, were the study designs adequate to guide physicians in the safe use of pramlintide in combination with insulin in
   a. Type 1 DM?
   b. Type 2 DM?

Not addressed.

Consider in particular with regard to the risk of hypoglycemia

i. during initiation of therapy (i.e., safe use in the early stages of therapy)
ii. during chronic therapy (i.e., adjustments of insulin and/or pramlintide dose)
iii. under conditions of strict glycemic control

Not addressed.

APPROVABILITY

5. Based on the data presented in the NDA and the adequacy of the trial designs, do you recommend approval of pramlintide for use in combination with insulin in
   a. Type 1 DM? **Yes – 1** **No - 8**
   b. Type 2 DM? **Yes – 3** **No - 6**

   If the answer to either of the above is no, what additional data would be required?

6. If the answer to either question in #5 is yes, please comment on the manner in which hypoglycemia risk should be addressed in labeling (e.g., bolded Warning, Black Boxed Warning, etc.).

Strong warning regarding anorexia, nausea and possible hypoglycemia

ADDITIONAL STUDIES

7. Regardless of your recommendations above, what additional studies do you recommend in patients with Type 1 and Type 2 DM for further address the safety, efficacy, or balance of risk and benefit of pramlintide?.

Incremental dosing and adjunct regimen
Augment previous therapy with triple therapy

Summary: The Committee expressed enthusiasm for the drug, believes it show promise and will be attractive to use. There is not enough information and requires more studies .

The meeting was adjourned at 4:30 pm.

Kathleen Reedy, RDH, MS, Health Scientist Administrator
Executive Secretary, Endocrinologic and Metabolic Drugs Advisory Committee