Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Silver Spring, 8777 Silver Spring, Maryland

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting for September 8, 2005

On September 8, 2005, the committee discussed new drug application (NDA) 21-868, proposed trade name Exubera (insulin recombinant deoxyribonucleic acid (rDNA) origin powder for oral inhalation), 1 milligram (mg) and 3 mg powder for inhalation, Pfizer, Inc., for the treatment of adult patients with diabetes mellitus

These summary minutes for the September 8, 2005 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on September 15, 2005.

I certify that I attended the September 8, 2005 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

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Paul D. Woolf, M.D.
(Acting) Chair

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
September 8, 2005
NDA 21-868 Exubera®
FINAL MINUTES

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

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 8, 2005, at the Holiday Inn, located at 8777 Georgia Avenue, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors.

The meeting was called to order by Paul Woolf, M.D., Acting Chair; the conflict of interest statement was read into the record by Cathy Groupe (Executive Secretary). Opening remarks were made by David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products. There were approximately 280 persons in attendance. There was one speaker for the Open Public Hearing session.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (voting)
Dean A. Follmann, Ph.D; Paul D. Woolf, M.D.; Sonia Caprio, M.D.; Nelson Watts, M.D. (non-voting for this meeting)

Endocrinologic and Metabolic Drugs Advisory Committee Consultants (voting):
Dara P. Schuster, M.D.; Rebecca W. Killion (Patient Representative)

Pulmonary-Allergy Advisory Committee Consultants (voting):
Talmadge E. King, M.D.; James K. Stoller, M.D.; William J. Calhoun, M.D.; Karen Schell (Consumer Representative)

Endocrinologic and Metabolic Drugs Advisory Committee Members Absent:
Michael R. McClung, M.D.; Jorge Plutzky, M.D.; Morris Schambelan, M.D.; Thomas O. Carpenter, M.D.; Steven W. Ryder, M.D. (Industry Representative); David S. Schade, M.D.; Margaret E. Wierman, M.D.

FDA Participants:
David Orloff, M.D.; Robert Meyer, M.D.; Karen Mahoney, M.D.; Sayed (Sam) Al Habet, R.Ph., Ph.D; Joy Mele, M.S.; Sally Seymour, M.D.

Open Public Hearing Speaker:
Marc Standberg, M.D.
Medical Director
Diabetes Health Center – Hunterdon Medical Center

Issue: New drug application (NDA) 21-868, proposed trade name Exubera (insulin recombinant deoxyribonucleic acid (rDNA) origin powder for oral inhalation), 1 milligram (mg) and 3 mg powder for inhalation, Pfizer, Inc., for the treatment of adult patients with diabetes mellitus.

The agenda proceeded as follows:
Sponsor Presentation
Pfizer Global Research and Development:

Introduction	Neville Jackson, M.D. Full Development Team Leader, EXUBERA Pfizer Global Research and Development
Overview of Clinical Program	Anne Cropp, Pharm.D. Global Clinical Leader, EXUBERA Pfizer Global Research and Development
Medical Need	William Cefalu, M.D. Professor and Chief, Department of Nutrition and Chronic Diseases Pennington Biomedical Research Center, LSU

Benefit and Managing the Risk	Neville Jackson, M.D. Pfizer Global Research and Development
	Committee Discussion
	Break

FDA Review Division Presentation:

Clinical Efficacy and Non-Pulmonary Safety Review	Karen M. Mahoney, M.D. Medical Officer FDA/CDER Division Metabolic and Endocrine Drug Products
Statistical Review and Evaluation	Joy D. Mele, M.S. Statistician FDA/CDER Office of Pharmacoepidemiology and Statistical Science
Clinical Pharmacology and Biopharmaceutics Review	Sayed (Sam) Al Habet, R.Ph., Ph.D. Senior Clinical Pharmacologist/Reviewer FDA/CDER Office of Clinical Pharmacology and Biopharmaceutics
Clinical Pulmonary Safety	Sally Seymour, M.D. Medical Officer FDA/CDER Division of Pulmonary and Allergy Drug Products
	Lunch
	Open Public Hearing
	Committee Discussion
	Break
	Committee Discussion and Questions to the Committee
	Adjournment

Questions to the Committee:

1. Efficacy in type 1 diabetes: Is there sufficient clinical trial evidence that Exubera® can be effectively applied to an "intensive" glycemic control regimen?

   YES: 8 NO: 1

2. Efficacy in type 2 diabetes: Has the efficacy of Exubera® been adequately assessed in patients with Type 2 diabetes?

   YES: 9 NO: 0

3. Hypoglycemia: Has the safety of Exubera® regarding hypoglycemia been adequately assessed?
   a. In Type 1 diabetes in "intensive" control regimens?

      YES: 7 NO: 2

   b. In Type 2 diabetes?

      YES: 9 NO: 0

4. Pulmonary effects:
   a. Are there sufficient data to assess the pulmonary safety of Exubera® in patients without underlying lung disease?

      YES: 9 NO: 0

i. If yes, do the data suggest an acceptable pulmonary safety profile in patients without underlying lung disease?

YES: 9 NO: 0

ii. If no, what additional information is needed?

b. Are there sufficient data to assess the pulmonary safety of Exubera® in patients with underlying lung disease?

YES: 4 NO: 5

i. If yes, do the data suggest an acceptable pulmonary safety profile in patients with underlying lung disease?
ii. If no, what additional information is needed?

Discussion: Committee concerns in regards to the pulmonary safety in patients with underlying lung disease included the need for additional studies such as a long-term study on interstitial lung disease and a substantially larger study in patients with chronic obstructive pulmonary disease that reflects the population of patients that will most likely be using this drug. The committee also commented on study design suggestions for both Study 1028 and 1030. (See transcript for detailed discussion).

5. Comments/discussion:
   a. Comment on clinical concerns and recommendations about the use of Exubera in the setting of pulmonary pathology or exogenous factors affecting pulmonary function:
      i. Viral upper respiratory infection
      ii. Asthma
      iii. COPD
      iv. Smoking

Discussion: There were general concerns about the use of Exubera in the setting of a viral upper respiratory infection. Asthma and COPD were also cited as concerns, specifically during their acute exacerbation stage and the challenges presented for clinicians in the care of these patients. The question of what will happen to patients in these settings needs to be addressed. Concerns about smoking were discussed, specifically passive smoking, including the lack of data on pharmacokinetics and pharmacodynamics associated with absorption and varying lung function. Additional comments included concerns about the necessity of a qualified professional to perform baseline spirometry in the clinical setting. (See transcript for detailed discussion).

b. Comment on clinical concerns and recommendations regarding dose adjustment (titration) and switching between inhaled and subcutaneous insulin.

Discussion: The suggestion was made to have the sponsor, rather than the patient, perform dose calculations, for an more exact titration with the primary concern centering on dosage equivalence and the patient population's familiarity with units given subcutaneously rather than milligram dosing.. With these concerns, there was further discussion about patient accountability for making these dosing decisions in the 'real world' setting and the subsequent confusion associated with titrating Exubera, such as a '3 X 1 mg' dose not being equal to a '1 X 3 mg' dose.

Additionally, the suggestion was made that intensive patient education is needed, specifically during titration periods, for patients to perform more frequent glucose monitoring. On the topic of patient education, there was further discussion identifying the challenges, in the clinical setting, of healthcare literacy and associated barriers to patient comprehension of what they are being prescribed. Clinicians are also confronted with the need to provide effective instructions to patients about the proper use of inhaled agents (i.e. metered-dose inhalers) on a regular basis (See transcript for detailed discussion).

c. Other issues

Discussion: The committee commented on the sponsor's post marketing plan, in terms of the need for an explicit plan about the signals in events such as cancer, that trigger consideration for post marketing review of these events. Additionally, concerns were raised about training for both new diabetics and those already using insulin. Questions were raised about resources the sponsor will have available for the vast array of training needs that will be required for educating patients about the proper use of this drug. The committee suggested that the sponsor demonstrate that they have a successful training program that "mirrors real life".

Additionally, the committee pointed out that Exubera will not 'replace' the need for bolus insulin, and the patient cannot throw away their insulin needle/syringe. The size of the device itself was identified as a problem, in terms of portability for the patient and problems associated with not having the device when insulin is needed. The practicality of the device was identified as an additional concern, in terms of patient utilization, specifically the stigma associated with using medication in a public setting. (See transcript for detailed discussion).

6. Should Exubera® be approved for the proposed indications?
   a. Type 1 diabetes

   YES: 7 NO: 2

   b. Type 2 diabetes as monotherapy, in combination with basal insulin, in combination with oral agents

   YES: 7 NO: 2

Discussion: Committee participants with reservations about Exubera approval, for both Type 1 and Type 2 diabetes, cited concerns about the need for additional outcomes data, as discussed earlier, as well as the training issues that will likely challenge clinicians and patients. (See transcripts for detailed discussion)

7. Additional investigations: What, if any, recommendations does the committee have for additional investigations of Exubera®?

Discussion: Committee participants identified possible concerns about antibody titers associated with insulin resistance. The Division added comments on this topic about patient control of their diabetes and the doses of insulin that they require. The Sponsor also provided additional insight about circulating antibody levels, current insulins available and insulin resistance.

Additional comments included the need for additional data on lung function in African Americans, given their lung function differs from other populations studied, and it is unclear if they will react differently to this drug. (See transcripts for detailed discussion)

The meeting adjourned at approximately 4:00 pm.

See transcripts for detailed discussion.