

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 1, 2005

FROM: David G. Orloff, M.D.
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TO: NDA 21-868
Exubera (insulin[rDNA origin] powder for inhalation)
Treatment of type 1 and type 2 diabetes mellitus

SUBJECT: Background and summary of issues for discussion at Advisory Committee meeting on September 8, 2005

Background

Exubera is native-sequence recombinant human insulin in a drug-device combination product for administration via inhalation. Several basic premises form the background for the consideration of this product for marketing approval. First, insulin itself is “safe and effective” for the treatment of diabetes mellitus, both type 1 and type 2. Second, if a proposed insulin product is active after being systemically absorbed then, dosed adequately, it will lower glucose and glycemic exposure in patients with diabetes. Third, different insulin preparations with differing properties (e.g., by pharmacokinetics, route of administration, or variability in dose delivered or systemic absorption) may in practice be fraught with greater or lesser risks of hypoglycemia for any degree of glycemic control. In short, critical to the approval of a given insulin product (e.g., depending upon pharmacokinetic and pharmacodynamic characteristics) is to learn how to use the insulin optimally in the treatment of diabetes, such that the product can be adequately labeled for safe and effective use. But, importantly, as a start, there are no mysteries regarding the pharmacology of Exubera. It is, quite simply, insulin, though administered via a new route.

With regard to trial design, it is perhaps notable that all trials of Exubera were open-label, active-controlled trials. Ideally, trials of new drugs are double-blind and placebo-controlled. This is not practical or advisable with insulin products for two reasons. The first is that even as insulin lowers glucose (the goal of therapy), it poses a risk for hypoglycemia (the exaggerated therapeutic effect—not toxicity). The second reason is that, because of the first, insulin dose must be adjusted to glycemic goals and avoidance of hypoglycemia. Therefore, because of the inexorable link between benefit and risk of insulin and because fixed dosing is for practical purposes impossible, if doctors and patients are blinded to treatment allocation, then patients can be expected either to achieve suboptimal glycemic control or to experience excessive hypoglycemia, or both. Stated differently, blinding of insulin trials is not necessary to inference of efficacy of insulin; on the other hand, blinding would not permit a valid assessment of hypoglycemic risks in real-world use because achievement of glycemic goals and simultaneous avoidance of hypoglycemia require titration, which itself can only be accomplished in the setting of open-label use. Finally, however, because such trials cannot be blinded, direct measures to

mitigate bias, for example in selection of patients to treatment groups or in the clinical management of patients by treatment group, may be necessary.

Principal objectives of the Exubera program

The objectives of the Exubera development program were several and included the following: First, the appropriate dose(s) of Exubera had to be determined, initially by comparison of acute kinetics and glucose disposal dynamics to short-acting SC insulins. Additionally, an extensive biopharmaceutics research program with Exubera characterized kinetic and dynamic variability with Exubera compared to SC insulin in relevant patient subgroups and also explored dose proportionality and dosage strength equivalence. Second, because of concerns about the variable kinetics of Exubera (related to device function and patient characteristics and performance), an extensive program of clinical trials in type 1 and type 2 diabetes comparing regimens using Exubera versus injected short-acting insulin was undertaken. Specifically, comparisons to SC insulin as monotherapy, as part of basal-bolus insulin therapy, and, in type 2 diabetes, in combination with oral hypoglycemic agents of several classes, were deemed necessary to characterize the hypoglycemia risk per glucose control of this novel drug-device combination. Critical to the interpretation of the findings of the trials regarding hypoglycemia is the achievement, trial-by-trial, of clinically meaningful and comparable reductions in glycemia in Exubera and comparator SC insulin treatment groups. These studies are discussed in detail in the FDA background documents by Drs. Al Habet, Mahoney, and Mele.

Finally, and critically, the acute and chronic direct pulmonary risks associated with the large quantities of insulin powder (along with the lactose excipient) inhaled by patients using Exubera for long-term treatment of their diabetes had to be assessed. In this vein, the risks in patients with existing lung disease also needed to be investigated, given the anticipated broad appeal of an inhaled insulin product and the fact that a large population burden (including patients with diabetes) of pulmonary disease, including chronic bronchitis, chronic obstructive pulmonary disease, and reactive airways disease, goes undiagnosed. At a minimum, it is necessary to determine whether there is a significant risk of acute, important pulmonary decompensation in such patients, who may choose to use Exubera despite labeled recommendations or who may inappropriately use it because of ignorance as to their existing pulmonary compromise. Dr. Seymour, of the FDA's Division of Pulmonary and Allergy Products, has conducted a thorough review of the pulmonary safety information submitted.

Of note, no formal studies in the pediatric age group were required to be included in the application due to uncertainties about pulmonary safety prior to having results in adults. A relatively small number of adolescents were included in the program. Only a single trial in patients with type 1 diabetes age 6 to 11 was conducted which included 61 children treated with inhaled insulin. There were no children under age 6 studied.

Central issues

The prospect of being able to use insulin while avoiding some (for those treated with basal-bolus insulin regimens) or all (for those on short-acting insulin alone) of the injections historically part and parcel of insulin therapy stands to appeal to many patients, family members, and physicians.

It is essential that we and they understand the benefits and risks of this novel drug-device combination.

In this light, and to summarize the foregoing, the central issues impacting FDA's regulatory decision regarding Exubera relate to:

1. Pulmonary safety in patients without and with existing pulmonary disease
2. Utility as an alternative short-acting insulin, perhaps particularly in regimens directed at "intensive" glycemic control
3. Safety regarding hypoglycemia, particularly in patients engaged in "intensive" insulin therapeutic regimens.
4. Use in populations with underlying acute or chronic pulmonary conditions (e.g., infectious, smoking) impacting the kinetics of insulin absorption from the lung
5. Use in young children with DM1.

We look forward to a fruitful discussion of this application on September 8.

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/s/

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MEDICAL OFFICER