INTRODUCTION

Diabetes mellitus comprises a group of metabolic diseases that are characterized by high levels of blood glucose.\(^1\) This marked hyperglycemia results from defects in insulin production, insulin action, or both. Chronic illness is associated with serious long-term complications such as organ damage, dysfunction, or failure, particularly of the eyes, kidneys, nerves, blood vessels, and heart.\(^1\,3\)

Diabetes affects approximately 20.8 million people in the U.S.\(^4\) The annual economic cost of diabetes is approximately $132 million and represents 11% of health care expenditures in the nation.\(^5\)

There are three general categories of diabetes: type-1, type-2, and gestational. A fourth classification is sometimes used to refer to specific types of diabetes caused by genetic defects, diseases of the pancreas, and drugs or chemicals.\(^6\)

Type-1 diabetes is a result of the destruction of beta cells within the pancreas, eventually leading to a total deficiency of insulin secretion.\(^1\,2\,6\)

Type-2 diabetes results from insulin resistance and a progressive defect in the pancreas, and drugs or chemicals.\(^6\)

Type-1 diabetes is a result of the destruction of beta cells within the pancreas, eventually leading to a total deficiency of insulin secretion.\(^1\,2\,6\)

Type-2 diabetes results from insulin resistance and a progressive defect involving insulin secretory response.\(^1\,2\,6\)

This type accounts for approximately 90% to 95% of all diagnosed cases of diabetes.\(^2\)

Gestational diabetes, diagnosed during pregnancy, is a form of glucose intolerance that can cause various complications in infants and mothers.\(^2\,6\)

A number of injectable insulin products and oral agents are available for the treatment of diabetes. In January 2006, a novel insulin product was approved by the U.S. Food and Drug Administration (FDA). Exubera (Pfizer) is the first (recombinant DNA origin) human insulin inhalation powder indicated for the control of hyperglycemia in adults with diabetes. It should be used along with a longer-acting insulin in patients with type-1 diabetes and may be used as monotherapy or in combination with oral agents (or longer-acting insulins) in patients with type-2 diabetes.\(^7\)

PHARMACOLOGY AND MECHANISM OF ACTION\(^7\,8\)

Exubera is the first inhaled insulin available in the U.S.; it provides an innovative system of delivering insulin. It is rapidly acting, with clinical effects identical to those of conventional insulin products that stimulate glucose uptake by skeletal muscle and fat in the periphery, inhibiting hepatic glucose production, resulting in lower blood glucose concentrations. In addition, insulin prevents fat and protein breakdown and enhances protein synthesis.

PHARMACOKINETICS AND PHARMACODYNAMICS\(^7\,9\)

Exubera is delivered via oral inhalation and is deposited in the lungs. In healthy subjects, this product has a rapid onset of activity that is comparable to that of the subcutaneous (SQ) rapidly acting insulin analogues and a duration of action that is comparable to that of SQ regularly acting insulin analogues. Therefore, after inhalation, the onset of action is approximately 10 to 20 minutes.

Maximum glucose-lowering activity occurs at two hours, and the duration of action is approximately six hours. The absorption of insulin following the inhalation of the powder is not dependent upon body mass index, as is the case with SQ insulin.

CLINICAL TRIALS

The safety and efficacy of Exubera have been demonstrated in various clinical trials.

Study A and Study B\(^7\)

Two 24-week, randomized, open-label, active-control studies were conducted to assess the safety and efficacy of inhaled insulin powder in patients with type-1 diabetes (Table 1). In Study A, one group of patients received inhaled insulin powder three times daily before meals plus a single injection of Ultralente insulin at night; the other group received SQ regular insulin twice daily before breakfast and before dinner plus long-acting human insulin (NPH). In Study B, one group of patients received inhaled insulin powder three times daily before meals plus twice-daily NPH insulin; the other group received SQ regular insulin three times daily before meals plus twice-daily NPH insulin in the morning and at bedtime.

In both studies, the reductions in glycylated hemoglobin (HbA\(_1c\)) levels, the percentage of patients reaching HbA\(_1c\) levels of below 8% or 7%, and the rates of hypoglycemia were comparable among the treatment groups. However, patients treated with inhaled insulin powder showed greater reductions in fasting plasma glucose (FPG) levels.

Hollander et al.\(^10\)

In another study, investigators compared inhaled insulin powder three times daily, taken before meals, along with a single bedtime dose of Ultralente insulin (n = 149) with a conventional regimen of at least two daily injections of SQ mixed (regular and NPH) insulin (n = 150) in a...
Patients with type-2 diabetes who were receiving no pharmacological therapy and who had suboptimal glucose control were randomly divided into two groups. One group (n = 76) received inhaled insulin powder three times daily before meals. The other group (n = 69) received rosiglitazone maleate (Avandia, GlaxoSmithKline) 4 mg twice daily for three months along with diet and exercise.

The primary endpoint was the percentage of patients who achieved HbA1c levels of below 8%. Levels of FPG and two-hour PPG were also evaluated as secondary endpoints.

At the end of the study, the proportion of patients who reached the HbA1c goal of below 8% was significantly higher with inhaled insulin powder (82.7%) than with rosiglitazone (58.2%). In addition, the proportions of patients achieving the American Diabetes Association’s HbA1c goal of below 7% and the American Association of Clinical Endocrinologists’ HbA1c goal of less than 6.5% were higher with inhaled insulin than with rosiglitazone (44% vs. 17.9% and 28% vs. 7.5%, respectively).

Mean changes from baseline FPG and PPG levels were found to be comparable among both treatment groups (–64 vs. –56 mg/dl and –92 vs. –92 mg/dl, respectively). Pulmonary function test results were comparable in both study groups. However, patients receiving inhaled insulin powder reported a greater number of hypoglycemic events.

ADVERSE DRUG REACTIONS

Adverse drug reactions observed with the use of inhaled insulin powder have been classified as respiratory and non-respiratory.

Non-respiratory symptoms included hypoglycemia, chest pain, dry mouth, and otitis media (in pediatric patients only). Incidence rates of hypoglycemia were similar in patients with type-1 and type-2 diabetes who received the inhaled insulin and in those receiving SQ regular human insulin.

In type-2 diabetic patients receiving oral single-agent therapy, the addition of Exubera was associated with an increased rate of hypoglycemia, compared with the addition of a second oral agent. Nonspecific chest pain was also reported, and 90% of these cases were described as mild or moderate. Dry mouth occurred in all patients receiving inhaled insulin therapy (98%) and was mild to moderate, although no patients discontinued therapy because of this side effect.

Respiratory adverse events included mainly cough and dyspnea. In most of

### Table 1 Results from Two Studies of Inhaled Insulin in Patients with Type-1 Diabetes

<table>
<thead>
<tr>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled Insulin</strong></td>
<td><strong>Regular Insulin</strong></td>
</tr>
<tr>
<td>+ Ultralente Insulin (n = 136)</td>
<td>+ NPH Insulin (n = 132)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (HbA1c)</td>
<td></td>
</tr>
<tr>
<td>• Baseline mean</td>
<td>7.9</td>
</tr>
<tr>
<td>• Mean change from baseline (adjusted)</td>
<td>–0.2</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>• Baseline mean</td>
<td>191</td>
</tr>
<tr>
<td>• Mean change from baseline (adjusted)</td>
<td>–32</td>
</tr>
<tr>
<td>Two-hour postprandial plasma glucose (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>• Baseline mean</td>
<td>283</td>
</tr>
<tr>
<td>• Mean change from baseline (adjusted)</td>
<td>–21</td>
</tr>
<tr>
<td>Patients with HbA1c below 8% at end of study</td>
<td>64%</td>
</tr>
</tbody>
</table>

the patients, cough associated with Exubera use was described as mild to moderate and usually occurred approximately 10 minutes after inhalation of the powder. Coughs were rarely productive, and they subsided with the continuation of therapy. Mild-to-moderate pharyngitis, increased sputum, and epistaxis were also reported.

In terms of the route of administration, pulmonary function is of great concern with the use of Exubera, particularly because insulin therapy is most often expected to be lifelong. The most extensive data on assessing pulmonary function in patients receiving inhaled insulin are available from some clinical trials that lasted for approximately two years. In these trials, treated patients displayed an increased loss of pulmonary function, specifically, in forced expiratory volume (FEV₁) and in carbon monoxide diffusing capacity (DLCO). Altered lung function was evident the first several weeks of therapy but subsequently stabilized during the remainder of the two-year treatment period studied.

One study showed that upon discontinuation of inhaled insulin therapy, FEV₁ returned to baseline values in type-2 diabetic patients. Overall, a decrease in FEV₁ of 20% or more from baseline occurred in 1.5% of patients (the rate was 1.3% for patients not treated with inhaled insulin), and a decrease in DLCO from baseline of 20% or more occurred in 5.1% of patients (the rate was 3.6% for those not using inhaled insulin).

**DRUG–FOOD INTERACTIONS**

Products administered via inhalation are of particular interest in assessments of interactions with inhaled insulin powder. Although inhaled medications and other products may alter the absorption of the powder, no specific data are available to support this possibility. Therefore, it is recommended that administration of other inhaled products be kept consistent with that of Exubera (i.e., in timing, schedules, and so on).

Many drugs may alter blood glucose metabolism, resulting in a change of insulin requirements when they are administered concomitantly with Exubera. Common medications that can increase the likelihood of hyperglycemia include corticosteroids, diuretics, sympathomimetic agents, protease inhibitors, atypical antipsychotic agents, estrogens, and thyroid hormones. As with conventional insulin therapy, beta blockers and clonidine (Catapres, Boehringer Ingelheim) are among the most common medications that may mask the signs and symptoms of hypoglycemia. Strict glucose monitoring is recommended in patients who take such drugs concomitantly with inhaled insulin.

**CONTRAINDICATIONS**

Exubera is contraindicated in patients who are hypersensitive to the product, or to any of its excipients, and in all patients who smoke or who have stopped smoking within six months of beginning therapy. Treatment should be discontinued immediately in individuals who begin smoking after starting therapy because of the increased risk of hypoglycemia. A more rapid onset of action, a greater maximum effect, and an increased glucose-lowering effect has been reported in smokers compared with non-smokers.

Inhaled insulin should not be used in patients with a history of unstable or poorly controlled lung disease. The instability and variation in lung function may affect the absorption of the medication, and hypoglycemia or hyperglycemia may result.

**PRECAUTIONS AND WARNINGS**

Patients receiving Exubera therapy must be monitored for pulmonary function. Baseline and follow-up pulmonary function tests are recommended to minimize potential pulmonary complications. The safety and efficacy of Exubera in patients with underlying lung disease, such as asthma or chronic obstructive pulmonary disease, have not been established.

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**Table 2** Approximate Guidelines for the Initial Pre-Meal Dose of Inhaled Insulin*

<table>
<thead>
<tr>
<th>Patient’s Weight (in Kilograms)</th>
<th>Patient’s Weight (in Pounds)</th>
<th>Initial Dose per Meal</th>
<th>No. of 1-mg Exubera Blisters per Dose</th>
<th>No. of 3-mg Exubera Blisters per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39.9 kg</td>
<td>66–87 lb</td>
<td>1 mg</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>40–59.9 kg</td>
<td>88–132 lb</td>
<td>2 mg</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>60–79.9 kg</td>
<td>133–176 lb</td>
<td>3 mg</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>80–99.9 kg</td>
<td>177–220 lb</td>
<td>4 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>100–119.9 kg</td>
<td>221–264 lb</td>
<td>5 mg</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>120–139.9 kg</td>
<td>265–308 lb</td>
<td>6 mg</td>
<td>—</td>
<td>2</td>
</tr>
</tbody>
</table>

* Based on the patient’s body weight.

Data from Exubera. Package insert. Pfizer Inc.; May 2006.7

**Table 3** Approximate Equivalents of Regular Human Subcutaneous (SQ) Insulin and Inhaled Insulin*

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Approximate Dose of Regular SQ Insulin (IU)</th>
<th>No. of 1-mg Exubera Blisters per Dose</th>
<th>No. of 3-mg Exubera Blisters per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>3</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>2 mg</td>
<td>6</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>3 mg</td>
<td>8</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>4 mg</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 mg</td>
<td>14</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6 mg</td>
<td>16</td>
<td>—</td>
<td>2</td>
</tr>
</tbody>
</table>

* Range, 1 to 6 mg.

Data from Exubera. Package insert. Pfizer Inc.; May 2006.7
Blisters are individually loaded into the 1-mg and 3-mg dose blisters (Table 2). Maintenance of the Exubera Inhaler:

• Clean the inhaler by hand at least once a week.
• Change the release unit every two weeks to help ensure that the correct dose is delivered.
• Replace the inhaler one year after the first use.


Dosage and Administration7–11

Inhaled insulin powder is supplied as 1-mg and 3-mg dose blisters (Table 2). Blisters are individually loaded into the dispenser and punctured, and the powder is inhaled by the patient through the mouth. Because of the powder’s rapidly acting, insulin-lowering effect, it should be administered no more than 10 minutes before a meal, three times a day.

Doses are individualized according to the needs of each patient. The beginning dose is based on the patient’s weight, current glycemic control, previous response to insulin, duration of diabetes, and dietary and exercise habits. Patients must properly monitor blood glucose levels by performing fingerstick tests in order to adjust insulin doses. Dose adjustments are based on individual patient responses and are dependent on meal size, nutrient composition, time of day, exercise schedule, and results of blood glucose monitoring.

Each 1-mg blister of inhaled insulin powder is approximately equivalent to 3 international units (IU) of subcutaneously administered regular human insulin (Table 3). Comparison of administration between three 1-mg blisters and one 3-mg blister resulted in a maximum concentration (Cmax) and in an area-under-the-curve (AUC) concentration that is 30% to 40% greater. Therefore, one blister dose should not be substituted for another. The 1-mg and 3-mg blister doses should be combined when other insulin doses are required in order to minimize the number of inhalations needed.

Instructions for administering the powder are presented in Table 4.

Table 4: Key Steps for Patients in Administering Inhaled Insulin Powder

1. Load the blister.
   • Pull the base out of the chamber using the black pull ring at the bottom until you hear a “click.”
   • Hold the Exubera blister with the notch pointed toward the inhaler. The printed side should be up.
   • Slide the blister into the slot as far as it will go.

2. Apply pressure.
   • Make sure that the mouthpiece is closed.
   • Pull out the blue handle from the bottom as far as it will go.
   • Squeeze the handle until it snaps shut (this puts pressure in the system).

3. Release the cloud.
   • Hold the inhaler so that the blue button faces you.
   • Press the blue button until it clicks.
   • A cloud of Exubera should fill the chamber.
   • After the cloud is in the chamber, do not delay inhaling your dose.

4. Inhale.
   • Stand or sit up straight, then breathe out normally.
   • Turn the mouthpiece around so it faces you. Promptly place the mouthpiece fully in your mouth, then form a seal around it with your lips.
   • In one breath, slowly and deeply breathe the cloud in through your mouth.
   • Take the mouthpiece out of your mouth. Close your mouth, and hold your breath for 5 seconds.
   • Breathe out normally.

After taking the dose:

• Turn the mouthpiece back to its closed position.
• Press the gray button to remove the blister. Some powder may be left in the blister. Place the unused blister in the household trash, secured away from children and pets.
• If you need to use more than one blister for your dose, repeat steps 1 through 4.
• When you finish, collapse the chamber to close your inhaler.

CONCLUSION

Diabetes is a chronic illness that calls for appropriate medical care and self-management education in order to prevent and reduce the risk of associated complications.6,14,15 Pharmacotherapeutic regimens, including various insulin products and oral agents, have been combined with diet and exercise plans to increase survival in diabetic patients.

Exubera is the first inhaled insulin powder to be approved in the U.S. and thus offers an alternative to conventional injectable insulins. This product may offer advantages to patients with a fear of needles and may increase compliance in certain patients reluctant to administer additional insulin injections.

Although inhaled insulin may have many potential benefits, additional studies are needed to examine its long-term consequences, particularly adverse effects involving pulmonary lung function.

REFERENCES

2. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC). National Diabetes Fact Sheet: General Information and


