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Exubera®

Treatment of Type 1 and Type 2 Diabetes

Inhaled, rapid-acting, dry-powder recombinant insulin formulation

EN: 229896

Abstract

Exubera® is an inhaled insulin formulation for patients with type 1 and insulin-requiring type 2 diabetes, the most advanced of several inhaled insulin systems being developed. It uses an inhalation device and inhaled insulin formulation process that is a noninvasive alternative to injections. Exubera® is associated with fewer systemic side effects and offers rapid symptom relief. The formulation has been studied in over 3,000 patients, some for as long as 6 years. Evidence suggests that Exubera® may be as effective as s.c. insulin and superior to oral agents in controlling glycemia in patients with diabetes. It appears to have a unique effect on both fasting plasma and 2-h postprandial glucose levels compared with other treatment regimens. The increased insulin antibodies that appear with Exubera® are not associated with any significant clinical manifestations. In clinical trials, the frequency and severity of adverse events were similar in the Exubera® and control groups. Although mild to moderate cough occurred more frequently in Exubera®-treated patients, it disappeared with increased exposure. A small difference in pulmonary function tests, without clinical manifestations, has been observed between Exubera® and control patients. Exubera® has been filed for approval in Europe and is expected to be submitted soon to the FDA.

Introduction

Over 177 million people worldwide have diabetes, and it is currently the fourth leading cause of death in most developed countries (1). Type 2 diabetes accounts for over 90% of diabetes cases and an estimated 50% of individuals with type 2 diabetes have inadequately controlled glycemia with oral agents. Uncontrolled diabetes is associated with significant morbidity and mortality. Insulin is the standard of care for people with type 1 diabetes, and over 30% of those with type 2 diabetes will eventually require insulin therapy. Treatment with insulin typically includes multiple daily injections, which is a considerable burden to many people. Adherence to such a regimen is often difficult to maintain, thereby compromising optimal glycemic control. Insulin delivery by injections is currently considered the most efficient and reliable way of delivering insulin to the bloodstream. However, several alternative means of insulin delivery have been considered, including the transdermal, oral, nasal, rectal, ocular, buccal, vaginal and uterine routes (2). The pulmonary route has received the most attention, owing to the recent development of inhaler devices and insulin formulation technology. A noninvasive alternative to insulin injections would be a major improvement in the treatment of insulin-requiring diabetes.

Several companies are developing devices for the pulmonary delivery of insulin, either as dry powder or liquid formulations. Dry powder aerosols are usually highly soluble and dissolve quickly in the fluid layer on the surface of the deep lung before passing through the thin single layer of the alveoli (3). The particles are 1-3 microns in diameter for optimum deep-lung delivery. Apart from the benefit of needleless administration, inhaled insulin enters the bloodstream more rapidly than by s.c. injection. This is likely to be especially beneficial when administering insulin just before meals, and may improve treatment compliance. This approach has the potential to allow subjects currently unwilling to accept multiple doses of injected insulin to achieve goals for optimal glycemic control.

A proof-of-concept study demonstrated the utility of Exubera® for controlling fasting and postprandial blood glucose concentrations (4, 5). Other clinical studies show that the formulation is effective and easy to use and associated with high patient satisfaction and acceptance. Exubera® is as effective as injected insulin and superior to oral agents in lowering blood glucose levels in patients with diabetes. Potential issues associated with inhaled insulin treatment include insulin antibody formation, altered insulin absorption caused by pulmonary disease and the possibility of infrequent direct adverse pulmonary effects. Inhaled insulin therapy is in the advanced clinical

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development stage, and longer term studies assessing the impact of Exubera® on several therapeutic scenarios and patient populations, with particular attention to safety and efficacy, are ongoing. The available clinical experience indicates that Exubera® has the potential to be an effective therapeutic option for patients with type 1 or type 2 diabetes.

Pharmacological Studies

Studies with Exubera® have shown that serum insulin concentrations peak earlier and decay more rapidly following inhalation compared with s.c. regular insulin. The hepatic and peripheral effects of inhaled *versus* s.c. insulin were investigated in conscious dogs. In 15 beagle dogs, somatostatin was administered to suppress endogenous insulin and glucagon was administered to maintain basal levels, while giving intraportal glucose loads in both groups. At matched plasma insulin levels, inhalation of human insulin as a dry powder was associated with a rapid rise in arterial insulin levels to a maximum concentration of 55 ± 6 μU/ml at 14 min with 1 mg insulin, and to 92 ± 9 μU/ml at 9 min with 2 mg insulin. The levels then declined over 3 h to those typical of conscious dogs fasted overnight. In contrast, 0.36 U/kg s.c. insulin was associated with a much slower rise in arterial plasma insulin levels, peaking at 55 ± 8 μU/ml by 64 min before gradually returning to baseline levels by 6 h. Portal insulin levels increased in all groups tested, with the greatest increase in the animals receiving 2 mg inhaled insulin. Peak portal insulin levels for s.c. insulin were comparable to those for 1 mg inhaled insulin and significantly less than those for 2 mg inhaled insulin. However, the portal area under the curve (AUC) observed with 2 mg inhaled insulin was not significantly different from that observed with s.c. insulin, and significantly greater than that for 1 mg inhaled insulin. Deep venous insulin levels also rose rapidly in response to both doses of inhaled insulin after 34 and 19 min, respectively, and then declined to baseline by 3 h. In contrast, deep venous insulin levels rose more slowly, peaking at 64 min, with s.c. insulin and gradually declining to baseline by 6 h. Surprisingly, about 20% more glucose was required to maintain euglycemia in the 2 mg inhaled insulin group compared with the s.c. insulin group. Taken together, these findings suggest a better overall glycemic effect of inhaled insulin compared with s.c. insulin (6).

Clinical Studies

Results from both short- and long-term clinical trials indicate that Exubera® is effective and well tolerated in controlling blood glucose levels in patients with type 1 diabetes, insulin-requiring type 2 diabetic patients and uncontrolled type 2 diabetic patients.

A 6-month phase III study involving 335 patients with type 1 diabetes between the ages of 12 and 65 years was designed to evaluate whether an insulin regimen containing preprandial Exubera® plus a single injection of long-acting insulin at bedtime could provide glycemic control similar to 2-3 insulin injections a day. Inhaled insulin was delivered as 1-2 inhalations of 1 or 3 mg before meals. Glycosylated hemoglobin (HbA1c) levels were reduced to a similar degree in patients in the Exubera® (7.9-8.1%) and conventional insulin groups (7.7-8.1%). An HbA1c value of < 7-8% was achieved in a similar number of patients from both treatment groups. The reductions in both fasting plasma glucose and 2-h postprandial glucose concentrations were significantly greater for patients using inhaled insulin compared to those given conventional insulin injections. Patients in the study preferred using Exubera® and experienced fewer hypoglycemic events compared to patients using insulin injections alone. In addition, patients receiving Exubera® reported significant improvements in overall treatment satisfaction and quality of life, as well as more favorable improvements in symptoms such as depression, well-being and cognitive function, according to a Diabetes Quality of Life and Treatment Satisfaction Questionnaire. Weight gain was also significantly less in patients taking Exubera®. The frequency and nature of adverse events reported in the study were comparable in both groups. However, mild to moderate cough was reported more frequently in patients taking Exubera® (27% *versus* 5%), but decreased in incidence and prevalence over the course of the study. A small difference in pulmonary function was observed between the treatment groups (7).

The findings from this trial confirm and extend those of an earlier proof-of-concept study in 73 patients with type 1 diabetes. The reductions in HbA1c concentrations were similar in patients receiving preprandial Exubera® plus 1 s.c. insulin injection at bedtime and those receiving their usual regimen of 2-3 insulin injections per day. Changes in both fasting plasma glucose and postprandial glucose concentrations were not significantly different between the treatment arms. The occurrence and severity of hypoglycemia were also similar for both groups. Inhaled insulin was well tolerated and there were no significant effects on pulmonary function (8).

A 1-year-follow-up analysis (9) was performed on the above-mentioned study (8) and another short-term study of glycemic control in diabetic patients (10). The parent studies were 3-month randomized trials comparing the efficacy of preprandial inhaled insulin plus 1 insulin injection at bedtime with 2-3 regular s.c. insulin injections a day in 70 patients with type 1 diabetes and 26 patients with type 2 diabetes. At 1 year, inhaled insulin was associated with greater reductions in HbA1c than conventional s.c. injections. Greater overall satisfaction was also achieved in patients receiving inhaled insulin compared to those receiving regular insulin injections (9).

The efficacy of inhaled insulin was analyzed from the findings of 3 multicenter, open-label, randomized, parallel-group phase III trials (11). The first study compared preprandial inhaled insulin plus 1 insulin injection at bedtime with 2-3 injections of s.c. insulin in type 2 diabetic

patients (12). The second study compared preprandial inhaled insulin with preprandial inhaled insulin plus an oral agent, or continued oral agent alone in type 2 diabetic patients uncontrolled on oral therapy (13). The third study compared preprandial inhaled insulin with rosiglitazone in type 2 diabetic patients uncontrolled on diet and exercise (14). An analysis of these studies showed that, despite comparable HbA1c concentrations at baseline, significantly more patients receiving inhaled insulin achieved the European Diabetes Policy Group HbA1c concentration treatment goal of 6.5% or less compared to those receiving other regimens.

A 3-month randomized, controlled trial and the combined results of two 6-month studies in patients with poorly controlled type 2 diabetes demonstrated improved efficacy for Exubera® when combined with oral agents (5, 15). In all studies, blood glucose levels were poorly controlled despite therapy with metformin or a sulfonylurea. In the first study, 68 patients were randomized to either adjunctive Exubera® or to continue taking their prestudy oral therapy for 3 months. Preprandial inhaled insulin was delivered in 1-2 inhalations of 1 or 3 mg. The mean reduction in HbA1c was significantly greater for the adjunctive Exubera® group than for the oral therapy group (2.3% *versus* 0.1%; $p < 0.001$). In addition, significantly more patients receiving Exubera® achieved HbA1c levels < 7% compared with those not receiving Exubera® (34% *versus* 0%). The addition of Exubera® to oral therapy resulted in a significantly greater reduction in fasting plasma glucose concentrations of 60.69 mg/dl ($p < 0.001$), and a significantly lower postprandial increase in glucose concentrations ($p = 0.02$). Exubera® treatment was associated with 1 severe hypoglycemic event, a greater increase in body weight than with oral therapy alone, and no significant changes in pulmonary function. Thus, the addition of inhaled insulin to oral agents improved glycemic control in type 2 diabetic patients not adequately controlled by metformin or a sulfonylurea (5). In the second study, 912 patients who had received metformin or sulfonylurea treatment for 6 months were randomized to either adjunctive Exubera® or an additional oral agent (metformin or glibenclamide) for 18 months. A total of 158 patients on adjunctive inhaled insulin and 146 patients on combination oral agent treatment completed the 18-month extension study. The primary endpoint was pulmonary safety. Reductions in HbA1c at 3-18 months were greater in patients receiving adjunctive Exubera® compared to those receiving an additional oral agent (from 9.6% to 7.7% *versus* from 9.6% to 8.1%). The most common adverse event in the Exubera®-treated group was cough, which was considered to be transient and mild. The occurrence and severity of hypoglycemic events were significantly lower in the Exubera® group than in the control group. Small differences in pulmonary function were observed between the Exubera® and control treatment groups. Pulmonary function, as measured by forced expiratory volume in 1 s (FEV_1) and the carbon monoxide-diffusing capacity (DL_{CO}), declined in both groups during treatment. However, by week 24, the changes from baseline in FEV_1 and DL_{CO} were greater in patients receiving Exubera® than in those receiving insulin injections (adjusted difference in FEV_1 and DL_{CO} = –0.063 l/s and –0.275 ml/min/mmHg, respectively). There was no significant difference between the groups in pulmonary function 12 weeks after the 2-year treatment period. Thus, small differences in pulmonary function were observed between the treatment groups early after treatment initiation, but did not progress with 2 years of continued treatment (15).

The efficacy and safety results from an open-label extension trial of inhaled insulin in diabetic patients have also been reported. A total of 204 patients with type 1 diabetes, insulin-treated type 2 diabetes or type 2 diabetes uncontrolled on oral agents who had completed 3-month, randomized, controlled trials were included. Overall, 159 subjects elected to receive inhaled insulin over the long term, 89 of whom had been treated for at least 4 years. The mean concentration of HbA1c decreased from 8.71% at baseline to 8.23% after 4 years of treatment. The frequency of hypoglycemic events decreased from 2.58 episodes during the first month to 1.50 episodes/month after 4 years. There was a mean decrease of 0.057 l/year in FEV_1 and of 0.376 ml/min/mmHg/year in DL_{CO}. These rates were similar to those seen during 2 years of observation in 23 diabetic patients who were receiving either oral agents or s.c. insulin (0.071 l/year and 0.673 ml/min/mmHg/year, respectively). These results suggest that there is stable glycemic control and no evidence of adverse long-term pulmonary consequences with long-term inhaled insulin treatment (16).

Several studies have focused on the treatment satisfaction with inhaled insulin in type 2 diabetic patients with poorly controlled glycemia on oral agents. One study examined 470 patients who were poorly controlled on metformin monotherapy and randomized to either adjunctive preprandial Exubera® or glibenclamide for 6 months. Randomization was stratified according to HbA1c levels. Among patients with a high baseline HbA1c concentration (> 9.5%), Exubera® was associated with a significantly greater improvement in glycemic control from baseline and significantly greater overall patient satisfaction compared with adjunctive glibenclamide. An improvement in glycemic control was positively correlated with improvements in general perceived health, general health status and convenience (17).

In a related study, the addition of preprandial inhaled insulin or metformin was investigated in 423 sulfonylurea-treated patients with type 2 diabetes. Randomization was also stratified according to HbA1c levels. After 6 months of treatment, the mean concentrations of HbA1c decreased from 9.7% at baseline to 7.6% in patients receiving adjunctive Exubera® and to 7.8% in those receiving adjunctive metformin ($p = 0.025$). Treatment discontinuation occurred in significantly fewer patients receiving inhaled insulin compared to metformin (6% *versus* 11%; $p = 0.04$). The improvement in glycemic control was particularly marked for those with a high baseline HbA1c level (> 9.5%), with a decrease to 7.8% in the

inhaled insulin-treated patients compared to 8.3% with metformin-treated patients ($p = 0.01$). Overall quality-of-life scores improved similarly in both treatment groups. Overall satisfaction was 42% greater in patients receiving inhaled insulin than in those receiving metformin. However, there was significantly greater patient dissatisfaction with side effects (weight gain and hypoglycemia) in the Exubera® group compared with the metformin group (18).

A 3-month, open-label study specifically examined the issue of treatment satisfaction with inhaled insulin in patients with type 1 diabetes. Following the 3-month study, patients were randomized to either inhaled insulin or s.c. insulin for 1 year. A total of 82% of patients who were receiving inhaled insulin initially elected to continue their current treatment. Of those who elected to discontinue their current treatment, the main reason was the rigor of the clinical study protocol. The mean percentage improvement from baseline to week 12 in overall treatment satisfaction was significantly greater with inhaled insulin than with s.c. insulin (35.1% *versus* 10.6%; $p < 0.01$). Improvement in overall treatment satisfaction was related to improvements in glucose control; an improvement in HbA1c of 1% from baseline to week 12 was associated with a 9.7% improvement in overall satisfaction after adjusting for treatment regimen. Compared with s.c. insulin, inhaled insulin was significantly better with regard to ease of administration, comfort, convenience, time and dosing, flexibility of eating schedule and ease of taking insulin several times a day. These findings in type 1 diabetic patients confirm those reported in type 2 diabetic patients, indicating that inhaled insulin is the preferred treatment and provides substantially more improvement in patient satisfaction compared with regular s.c. insulin injections (19).

The potential acceptance of inhaled insulin as a treatment option for type 2 diabetes was investigated in patients from 7 countries. A total of 779 type 2 diabetic patients who were poorly controlled on diet or oral therapy (HbA1c = 8% or greater) were randomized to 2 groups (A and B). Both groups received educational information about currently available treatment options for diabetes, and in addition, group B received educational material about Exubera® as a potential treatment option. Patient choice of therapy was obtained by questionnaires. Significantly more patients in group B chose a treatment option that included insulin compared to those in group A (43.2% *versus* 15.5%, odds ratio = 4.16; $p < 0.0001$). Despite having a mean HbA1c concentration of 9.1%, 43.3% of patients in group A chose to make no change to their treatment program, compared to only 27.4% of those in group B (odds ratio = 0.49; $p < 0.0001$). The most frequently chosen treatment option in group B was Exubera® (35.3%) (20). Based on the data from this study, the same group of researchers investigated the short- and long-term health outcomes of patients using inhaled insulin (21). Health outcomes were simulated using the Economic Assessment of Glycemic control and Long-term Effects (EAGLE) model. After 10 years, patients in group B achieved a significantly greater improvement in glycemic control compared to those in group A (absolute HbA1c difference = 1.2%). This difference between the 2 groups in favor of group B was observed every year from year 1 to year 10. The cumulative incidence of severe hypoglycemic events was greater in group B than in group A (7.7/100 persons *versus* 5.4/100 persons). However, group B was associated with a lower incidence (events/100 persons) of cumulative complications, including microvascular events (272.2 *versus* 305.7), macrovascular events (18.1 *versus* 19.6) and mortality (37 *versus* 39.5). Taken together, the findings demonstrate that Exubera® results in greater potential acceptance of insulin therapy and improves both the short- and long-term health outcomes of poorly controlled type 2 diabetic patients.

The issue of whether postprandial glucose control is affected by the insulin antibodies that appear following administration of inhaled insulin was addressed in a study including 45 patients with type 1 diabetes who were randomized to NPH insulin b.i.d. and either s.c. regular insulin or inhaled insulin for 6 months. Insulin antibody levels increased only in the inhaled insulin group by 98 ± 140 μU/ml at 6 months. Despite this difference, the groups failed to show significant differences in glycemic patterns with standardized meal challenge tests or in glucose infusion rates (GIRs) during isoglycemic glucose clamp studies. There were no significant differences between the inhaled insulin group or the s.c. insulin group with respect to changes in HbA1c concentrations, changes in fasting blood glucose concentrations and the rate of hypoglycemic events. Thus, the increase in insulin antibodies associated with inhaled insulin does not appear to impact significantly on GIR pharmacodynamics or postprandial blood glucose control (22). Several other studies have also reported inhaled insulin-induced increases in insulin antibodies without significant clinical or laboratory changes (7, 12-14).

The within-subject variability in the absorption of inhaled insulin was investigated in elderly obese patients with type 2 diabetes. A randomized, crossover study was performed on 20 obese (mean body mass index = 33 kg/m^2) patients with a mean age of 72 years. Patients received either Exubera® 4 mg by inhalation or 12 IU of s.c. insulin after an overnight fast. The peak insulin concentration (C_{max}) with inhaled insulin was 70% higher and occurred earlier than with s.c. insulin. Systemic insulin exposure was 87% higher for inhaled insulin than for s.c. insulin over 2 h and was similar between the treatment groups over 6 h. Within-subject variability in these parameters with inhaled insulin was similar to or less than that with s.c. insulin (23).

Exubera® is presently under review by the E.U. regulatory authorities for the treatment of type 1 and type 2 diabetes and an NDA is in the final stages of preparation in the U.S. (24).

Sources

Nektar Therapeutics (US); Pfizer, Inc. (US); Sanofi-Aventis (FR).

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