Weight Maintenance: Worthy Goal in and of Itself

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SAN FRANCISCO — Helping patients—even overweight patients—to avoid gaining more weight is an important therapeutic goal by itself, Dr. Robert Baron said at a diabetes update sponsored by the University of California, San Francisco.

"It's very, very hard to get people to lose weight. Therefore, our priority in a large number of our patients should be to prevent further weight gain," said Dr. Baron, professor of medicine at the university. "In our society, the default position is to gain weight. You need to have a strategy even to maintain your weight, and that's especially true as you age."

Recent data support the classic goals of being as fit as possible at one's current weight, preventing weight gain, and then considering attempts at weight loss, he emphasized. Being overweight by itself is not necessarily a risk factor for mortality, other data show. The presence or absence of metabolic syndrome plays a key role in level of risk.

A 2005 meta-analysis of three National Health and Nutrition Examination Surveys (NHANES I, II, and III) found no increased risk for mortality in people who fit the conventional definition of overweight for white people—a body mass index of at least 25 kg/m^2 but less than 30—although the mortality risk did increase among the obese (those with BMIs of 30 and higher). The findings suggest that a wider range of weights should be considered "normal" and associated with best healthy outcomes, Dr. Baron said.

"This is controversial, but I think it creates a need for some humility and diagnostic uncertainty about people who are overweight," he added.

Although the prevalence of obesity has been increasing, the mortality risk associated with obesity decreased between the first of the three surveys (NHANES I) and the more recent NHANES III; however, this could be because of methodologic differences.

The presence of metabolic syndrome doubled the risk for mortality in normal-weight people, increased absolute risk of death by about 50% in overweight people, and increased risk of death by 13% in obese people, a separate 2005 study of 19,173 men found.

Patients who are overweight may not be at increased risk if they are metabolically normal, but the presence of metabolic syndrome or other signs of insulin resistance changes the clinical picture.

"Your BMI is your initial screening test, if you will, and evaluation of metabolic syndrome becomes your more accurate, second-level test to sort out which patients in the overweight category and Class I obese [BMI of at least 30 but lower than 35] need more particularly aggressive interventions," he said.

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DR. BARON

Eating less and exercising are still the mainstays of weight loss strategies but must be pursued with greater intensity than many people realize if weight loss is to be the result.

Exercise alone won't do it, and casually "watching what you eat" won't work for most patients. Weight loss requires a diet of "low calories, low calories, low calories" that usually must be monitored quantitatively by the dieter, Dr. Baron advised. Combining calorie restriction with exercise and behavioral therapy traditionally offers the best approach.

Patients who do diet and exercise drop a mean of 8% of their original body weight in the first year, although some patients lose more and some gain weight instead, he added.

In addition, patients who have lost weight need a disciplined strategy to maintain that weight loss, data suggest.

Data on 3,000 successful dieters (mostly white women) who enrolled in the National Weight Control Registry and maintained a 30-pound or greater weight loss for 1 year showed three key steps to keeping the pounds off: high levels of physical activity, diets low in fat and high in fiber, and regular self-monitoring of weight. ■

Brief summary of full prescribing information.

EXUBERA®

(insulin human [rDNA origin]) Inhalation Powder

EXUBERA® Inhaler

Rx only

INDICATIONS AND USAGE

EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA has an onset of action similar to rapid-acting insulin analogs and has a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. In patients with type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. In patients with type 2 diabetes, EXUBERA can be used as monotherapy or in combination with oral agents or longer-acting insulins.

CONTRAINDICATIONS

EXUBERA is contraindicated in patients hypersensitive to EXUBERA or one of its excipients. EXUBERA is contraindicated in patients who smoke or who have discontinued smoking less than 6 months prior to starting EXUBERA therapy. If a patient starts or resumes smoking, EXUBERA must be discontinued immediately due to the increased risk of hypoglycemia, and an alternative treatment must be utilized. The safety and efficacy of EXUBERA in patients who smoke have not been established.

EXUBERA is contraindicated in patients with unstable or poorly controlled lung disease, because of wide variations in lung function that could affect the absorption of EXUBERA and increase the risk of hypoglycemia or hyperglycemia.

WARNINGS

EXUBERA differs from regular human insulin by its rapid onset of action. When used as mealtime insulin, the dose of EXUBERA should be given within 10 minutes before a meal.

Hypoglycemia is the most commonly reported adverse event of insulin therapy, including EXUBERA. The timing of hypoglycemia may differ among various insulin formulations.

Patients with type 1 diabetes also require a longer-acting insulin to maintain adequate glucose control.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analogs), or species (animal, human) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

Glucose monitoring is recommended for all patients with diabetes.

Because of the effect of EXUBERA on pulmonary function, all patients should have pulmonary function assessed prior to initiating therapy with EXUBERA.

The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety and efficacy of EXUBERA in this population have not been established.

PRECAUTIONS

General: As with all insulin preparations, the time course of EXUBERA action may vary in different individuals or at different times in the same individual. Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Hypoglycemia: As with all insulin preparations, hypoglycemic reactions may be associated with the administration of EXUBERA. Rapid changes in serum glucose concentrations may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment: Studies have not been performed in patients with renal impairment. As with other insulin preparations, the dose requirements for EXUBERA may be reduced in patients with renal impairment.

Hepatic Impairment: Studies have not been performed in patients with hepatic impairment. As with other insulin preparations, the dose requirements for EXUBERA may be reduced in patients with hepatic impairment.

Allergy

Systemic Allergy: In clinical studies, the overall incidence of allergic reactions in patients treated with EXUBERA was similar to that in patients using subcutaneous regimens with regular human insulin. As with other insulin preparations, rare, but potentially serious, generalized allergy to insulin may occur, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reactions, may be life threatening. If such reactions occur from EXUBERA, EXUBERA should be stopped and alternative therapies considered.

Antibody Production: Insulin antibodies may develop during treatment with all insulin preparations including EXUBERA. In clinical studies of EXUBERA where the comparator was subcutaneous insulin, increases in insulin antibody levels (as reflected by assays of insulin binding activity) were significantly greater for patients who received EXUBERA than for patients who received subcutaneous insulin only. No clinical consequences of these antibodies were identified over the time period of clinical studies of EXUBERA; however, the long-term clinical significance of this increase in antibody formation is unknown.

Respiratory

Pulmonary Function: In clinical trials up to two years duration, patients treated with EXUBERA demonstrated a greater decline in pulmonary function, specifically the forced expiratory volume in one second (FEV_1) and the carbon monoxide diffusing capacity (DL_{CO}), than comparator-treated patients. The mean treatment group difference in pulmonary function favoring the comparator group, was noted within the first several weeks of treatment with EXUBERA, and did not change over the two year treatment period. During the controlled clinical trials, individual patients experienced notable declines in pulmonary function in both treatment groups. A decline from baseline FEV_1 of ≥20% at last observation occurred in 1.5% of EXUBERA-treated and 1.3% of comparator-treated patients. A decline from baseline DL_{CO} of ≥20% at last observation occurred in 5.1% of EXUBERA-treated and 3.6% of comparator treated patients. Because of the effect of EXUBERA on pulmonary function, all patients should have spirometry (FEV_1) assessed prior to initiating therapy with EXUBERA. Assessment of DL_{CO} should be considered. The efficacy and safety of EXUBERA in patients with baseline FEV_1 or DL_{CO} <70% predicted have not been established and the use of EXUBERA in this population is not recommended.

Assessment of pulmonary function (e.g., spirometry) is recommended after the first 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms. In patients who have a decline of ≥20% in FEV_1 from baseline, pulmonary function tests should be repeated. If the ≥20% decline from baseline FEV_1 is confirmed, EXUBERA should be discontinued. The presence of pulmonary symptoms and lesser declines in pulmonary function may require more frequent monitoring of pulmonary function and consideration of discontinuation of EXUBERA.

Underlying Lung Disease: The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the efficacy and safety of EXUBERA in this population have not been established.

Bronchospasm: Bronchospasm has been rarely reported in patients taking EXUBERA. Patients experiencing such a reaction should discontinue EXUBERA and seek medical evaluation immediately. Re-administration of EXUBERA requires a careful risk evaluation, and should only be done under close medical monitoring with appropriate clinical facilities available.

Intercurrent Respiratory Illness: EXUBERA has been administered to patients with intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections, rhinitis) during clinical studies. In patients experiencing these conditions, 3-4% temporarily discontinued EXUBERA therapy. There was no increased risk of hypoglycemia or worsened glycemic control observed in EXUBERA-treated patients compared to patients treated with subcutaneous insulin. During intercurrent respiratory illness, close monitoring of blood glucose concentrations, and dose adjustment, may be required.

Drug Interactions: A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may reduce the blood glucose-lowering effect of insulin that may result in hyperglycemia: corticosteroids, danazol, diazoxide, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors, and atypical antipsychotic medications (e.g., olanzapine and clozapine).

The following are examples of substances that may increase the blood glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or reduce the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs and symptoms of hypoglycemia may be reduced or absent.

Bronchodilators and other inhaled products may alter the absorption of inhaled human insulin. Consistent timing of dosing of bronchodilators relative to EXUBERA administration, close monitoring of blood glucose concentrations and dose titration as appropriate are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies in animals have not been performed. Insulin was not mutagenic in the Ames bacterial reverse mutation test in the presence and absence of metabolic activation. In Sprague-Dawley rats, a 6-month repeat-dose toxicity study was conducted with insulin inhalation powder at doses up to 5.8 mg/kg/day (compared to the clinical starting dose of 0.15 mg/kg/day, the rat high dose was 39 times or 8.3 times the clinical dose, based on either a mg/kg or a mg/m^2 body surface area comparison). In Cynomolgus monkeys, a 6-month repeat-dose toxicity study was conducted with inhaled insulin at doses up to 0.64 mg/kg/day. Compared to the clinical starting dose of 0.15 mg/kg/day, the monkey high dose was 4.3 times or 1.4 times the clinical dose, based on either a mg/kg or a mg/m^2 body surface area comparison. These were maximum tolerated doses based on hypoglycemia. Compared to control animals, there were no treatment-related adverse effects in either species on pulmonary function, gross or microscopic morphology of the respiratory tract or bronchial lymph nodes. Similarly, there was no effect on cell proliferation indices in alveolar or bronchiolar area of the lung in either species. Because recombinant human insulin is identical to the endogenous hormone, reproductive/fertility studies were not performed in animals.

Pregnancy - Teratogenic Effects - Pregnancy Category C: Animal reproduction studies have not been conducted with EXUBERA. It is also not known whether EXUBERA can cause fetal harm when administered to a pregnant woman or whether EXUBERA can affect reproductive capacity. EXUBERA should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when EXUBERA is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in EXUBERA dose, meal plan, or both.

Pediatric Use: Long-term safety and effectiveness of EXUBERA in pediatric patients have not been established.

Geriatric Use: In controlled Phase 2/3 clinical studies (n=1975), EXUBERA was administered to 266 patients ≥65 years of age and 30 patients ≥75 years of age. The majority of these patients had type 2 diabetes. The change in HbA_{1c} and rate of hypoglycemia did not differ by age.

ADVERSE REACTIONS

The safety of EXUBERA alone, or in combination with subcutaneous insulin or oral agents, has been evaluated in approximately 2500 adult patients with type 1 or type 2 diabetes who were exposed to EXUBERA. Approximately 2000 patients were exposed to EXUBERA for greater than 6 months and more than 800 patients were exposed for more than 2 years.

Non-Respiratory Adverse Events:

Non-respiratory adverse events reported in ≥1% of 1977 EXUBERA-treated patients in controlled Phase 2/3 clinical studies, regardless of causality, include (but are not limited to) the following:

Metabolic and Nutritional: hypoglycemia (see WARNINGS and PRECAUTIONS)

Body as a whole: chest pain

Digestive: dry mouth

Special senses: otitis media (type 1 pediatric diabetics)

Hypoglycemia: The rates and incidence of hypoglycemia were comparable between EXUBERA and subcutaneous regular human insulin in patients with type 1 and type 2 diabetes. In type 2 patients who were not adequately controlled with single oral agent therapy, the addition of EXUBERA was associated with a higher rate of hypoglycemia than was the addition of a second oral agent.

Chest Pain: A range of different chest symptoms were reported as adverse reactions and were grouped under the non-specific term chest pain. These events occurred in 4.7% of EXUBERA-treated patients and 3.2% of patients in comparator groups. The majority (>90%) of these events were reported as mild or moderate. Two patients in the EXUBERA and one in the comparator group discontinued treatment due to chest pain. The incidence of all-causality adverse events related to coronary artery disease, such as angina pectoris or myocardial infarction was comparable in the EXUBERA (0.7% angina pectoris; 0.7% myocardial infarction) and comparator (1.3% angina pectoris; 0.7% myocardial infarction) treatment groups.

Dry Mouth: Dry mouth was reported in 2.4% of EXUBERA-treated patients and 0.8% of patients in comparator groups. Nearly all (>98%) of dry mouth reported was mild or moderate. No patients discontinued treatment due to dry mouth.

Ear Events in Pediatric Diabetics: Pediatric type 1 diabetics in EXUBERA groups experienced adverse events related to the ear more frequently than did pediatric type 1 diabetics in treatment groups receiving only subcutaneous insulin. These events included otitis media (EXUBERA 6.5%; SC 3.4%), ear pain (EXUBERA 3.9%; SC 1.4%), and ear disorder (EXUBERA 1.3%; SC 0%).

Respiratory Adverse Events:

The table below shows the incidence of respiratory adverse events for each treatment group that were reported in ≥1% of any treatment group in controlled Phase 2 and 3 clinical studies, regardless of causality.

Adverse Event	Percent of Patients Reporting Event				
	Type 1 Diabetes		Type 2 Diabetes		
	EXUBERA N = 698	SC N = 705	EXUBERA N = 1279	SC N = 488	OAs N = 644
Respiratory Tract Infection	43.3	42.0	29.2	38.1	19.7
Cough Increased	29.5	8.8	21.9	10.2	3.7
Pharyngitis	18.2	16.6	9.5	9.6	5.9
Rhinitis	14.5	10.9	8.8	10.5	3.0
Sinusitis	10.3	7.4	5.4	10.0	2.3
Respiratory Disorder	7.4	4.1	6.1	10.2	1.7
Dyspnea	4.4	0.9	3.6	2.5	1.4
Sputum Increased	3.9	1.3	2.8	1.0	0.5
Bronchitis	3.2	4.1	5.4	3.9	4.0
Asthma	1.3	1.3	2.0	2.3	0.5
Epistaxis	1.3	0.4	1.2	0.4	0.8
Laryngitis	1.1	0.4	0.5	0.4	0.3
Pneumonia	0.9	1.1	0.9	1.6	0.6
Voice Alteration	0.1	0.1	1.3	0.0	0.3

SC = subcutaneous insulin comparator; OA = oral agent comparators

Cough: In 3 clinical studies, patients who completed a cough questionnaire reported that the cough tended to occur within seconds to minutes after EXUBERA inhalation, was predominantly mild in severity and was rarely productive in nature. The incidence of this cough decreased with continued EXUBERA use. In controlled clinical studies, 1.2% of patients discontinued EXUBERA treatment due to cough.

Dyspnea: Nearly all (>97%) of dyspnea was reported as mild or moderate. A small number of EXUBERA-treated patients (0.4%) discontinued treatment due to dyspnea compared to 0.1% of comparator-treated patients.

Other Respiratory Adverse Events – Pharyngitis, Sputum Increased and Epistaxis: The majority of these events were reported as mild or moderate. A small number of EXUBERA-treated patients discontinued treatment due to pharyngitis (0.2%) and sputum increased (0.1%); no patients discontinued treatment due to epistaxis.

Pulmonary Function: The effect of EXUBERA on the respiratory system has been evaluated in over 3800 patients in controlled phase 2 and 3 clinical studies (in which 1977 patients were treated with EXUBERA). In randomized, open-label clinical trials up to two years duration, patients treated with EXUBERA demonstrated a greater decline in pulmonary function, specifically the forced expiratory volume in one second (FEV_1) and the carbon monoxide diffusing capacity (DL_{CO}), than comparator treated patients. The mean treatment group differences in FEV_1 and DL_{CO}, were noted within the first several weeks of treatment with EXUBERA, and did not progress over the two year treatment period. In one completed controlled clinical trial in patients with type 2 diabetes following two years of treatment with EXUBERA, patients showed resolution of the treatment group difference in FEV_1 six weeks after discontinuation of therapy. Resolution of the effect of EXUBERA on pulmonary function in patients with type 1 diabetes has not been studied after long-term treatment.

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild to moderate episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. Severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

EXUBERA doses should be administered immediately prior to meals (no more than 10 minutes prior to each meal). In patients with type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. For patients with type 2 diabetes, EXUBERA may be used as monotherapy or in combination with oral agents or longer-acting insulin.

A 1 mg blister of EXUBERA inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected regular human insulin. A 3 mg blister of EXUBERA inhaled insulin is approximately equivalent to 8 IU of subcutaneously injected regular human insulin.

Consecutive inhalation of three 1 mg unit dose blisters results in significantly greater insulin exposure than inhalation of one 3 mg unit dose blister. Therefore, three 1 mg doses should not be substituted for one 3 mg dose.

Please see EXUBERA full prescribing information and* EXUBERA Medication Guide *at www.exubera.com

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Revised July 2006.