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New Drug Update

A novel rapid - acting oral inhalation human insulin for diabetes mellitus: Afrezza

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ABSTRACT

Afrezza is rapid-acting oral inhalation insulin that is administered at the beginning of each meal. The U.S Food and Drug Administration has approved Afrezza (insulin human) inhalation powder, a rapid-acting inhaled insulin to improve glycemic control in adults ≥18 years of age with Type 1 or Type 2 diabetes mellitus (T1DM or T2DM). Afrezza must be used in combination with long-acting insulin in patients with T1DM. Afrezza may be used with either oral anti-diabetic drugs or basal insulin in patients with T2DM. Afrezza should be administered via oral inhalation using Afrezza inhaler. Dosage adjustment is needed when switching from injection insulin to oral inhalation Afrezza. It is contraindicated in individuals with chronic lung disease and smokers because of the risk of the acute bronchospasm. Before initiating, Afrezza, a complete medical history, physical examination and spirometry (forced expiratory volume 1 sec) results is required in all individuals to identify the potential lung disease. Common adverse reactions in individuals treated with Afrezza include hypoglycemia, cough, throat pain or irritation, headache, and diarrhea.

Keywords: Afrezza, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Rapid-acting human insulin analog, Regular-human insulin

INTRODUCTION

Inhalation human insulin promises to be rapid-acting and more convenient than traditional insulin injections, but an inhaled product has failed in the past and there are concerns about the potential risks associated with breathing powdered insulin. Inhalational insulin (Exubera) was approved in 2006 with big expectations but the inhaler was bulky, and patients were put off by the need for periodic lung function tests and eventually it was withdrawn.[1] Afrezza is manufactured by Mannkind Corp and distributed by Sanofi-Aventis. It is the only inhalable insulin and competes with traditional injectable insulin of Eli Lilly and Novo Nordisk. Afrezza inhalational powder is novel rapid-acting human insulin with a whistle-sized inhaler to control blood-sugar levels in both Type 1 and Type 2 diabetes mellitus (T1DM and T2DM).[2] It was developed in the shadow of inhalational insulin (Exubera) and approved by the U.S. Food and Drug Administration in June, 2014.

DRUG DESCRIPTION

Afrezza is supplied as single-use plastic cartridges filled with dry white powder of human insulin as 4 units or 8 units. The cartridges are color-coded, blue for 4 units and green for 8 units. The 4 units insulin contains 0.35 mg of insulin and 8 units contain 0.7 mg of insulin. It is administered as single oral-inhalation per cartridge at the beginning of a meal via Afrezza Inhaler only. The Afrezza Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, Afrezza inhaler must be discarded and replaced with

new inhaler. Afrezza contains human insulin produced by DNA recombinant technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin is adsorbed onto carrier particles consisting of fumaryl diketopiperazine and polysorbate 80.[3]

Indications

It has been recently approved by the US Food and Drug Administration and indicated for use in adults ≥18 years of age with T1DM or T2DM. In patients with Type 1 diabetes, must use with a long-acting insulin.[4] It is not a substitute for long-acting insulin.

Dosage

Dose adjustments are needed when switching from insulin to Afrezza. Insulin naïve individuals should start on 4 units of Afrezza at each meal. Those individual using subcutaneous insulin should estimate the total daily insulin dose. Administer half of the total insulin dose as long-acting basal insulin. Another half of the total insulin dose is divided equally among the three meal insulin dose. Convert the estimated mealtime insulin dose to an appropriate Afrezza insulin dose using Table 1. Dosing must be individualized based on metabolic needs and glycemic control required. Blood glucose control is carefully monitored in individual requiring higher doses of Afrezza. If glycemic control is not achieved even with higher doses of Afrezza, consider using subcutaneous mealtime insulin.

PHARMACODYNAMICS

Mechanism of action

Insulin lowers the blood sugar by stimulating peripheral uptake of glucose by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in adipocytes, inhibits proteolysis, and enhances protein synthesis.[5] In a study of 32 healthy subjects, the pharmacodynamic effect of Afrezza, measured as area under curve (AUC) the glucose infusion rate-time from a euglycemic clamp increased in a less than dose-proportional manner. This effect has been observed for subcutaneously administered insulins, but it is not sure if the diminishing pharmacodynamic benefit at a higher dosage of Afrezza parallels that which is seen with subcutaneously administered insulin. The pharmacodynamic profile of Afrezza oral inhalation insulin 8 units has been compared to subcutaneously administered insulin lispro 8 units in 12 patients with T1DM showed that the median time to maximum effect of Afrezza (measured by the peak rate of glucose infusion) was approximately 53 mins and the effect then declined to baseline by 160 mins. Afrezza has been studied in adults with T1DM in combination with basal insulin. The efficacy of Afrezza in T1DM is compared to insulin aspart in combination with basal insulin. At weeks 24, treatment with basal insulin and mealtime Afrezza provided a mean reduction in glycated hemoglobin (HbA1c) that met the pre-specified non-inferiority margin of 0.4%. Afrezza provided less HbA1c reduction than insulin aspart and the difference was statistically significant. More subjects in the insulin aspart group achieved the Hb1Ac target of <7%. T2DM patients poorly controlled on maximum tolerated doses of metformin only or more oral anti-diabetic drugs (OAD) participated in a 24 weeks, double-blind, and placebo controlled study. At weeks 24, treatment with Afrezza plus OAD provided a mean reduction in Hb1Ac that was statistically significantly greater compared to the Hb1Ac reduction in the placebo group.[6]

Table 1: Mealtime dose conversion.

Injected mealtime insulin dose (units)	Afrezza dose (units)
Up to 4	4
5-8	8
9-12	12
13-16	16
17-20	20
21-24	24

PHARMACOKINETICS

Insulin contained in Afrezza is regular insulin. Following pulmonary absorption into systemic circulation, the metabolism and elimination are comparable to regular insulin. The maximum serum insulin concentration was reached by 12-15 mins after oral inhalation of Afrezza units and serum insulin concentration was reduced to baseline after 180 mins. The median terminal half-life following oral inhalation of Afrezza 4 and 32 units was 28-39 mins, and 145 mins for subcutaneously regular human insulin (RHI) 15 units. Clinical pharmacology studies showed that carrier particles are not metabolized and are eliminated unchanged in the urine following the lung absorption. Albuterol (salbutamol) increased the area under curve (AUC) insulin administered by Afrezza by 25% in patients with bronchial asthma.[7]

CLINICAL STUDIES

In clinical studies 3017 patients were treated with Afrezza, of which 1026 were of T1DM and 1991 were of T2DM. The mean exposure duration was 8.16 months and 8.18 months for T1DM and T2DM respectively. Afrezza was studies in placebo and active- controlled studies (n=3 and n=10 respectively). The mean age of the population was 50.2 years and 50.8% were men. At baseline, T1DM had diabetes for an average of 16.6 years and a mean Hb1Ac of 8.3%, T2DM had diabetes for an average of 10.7 years and a mean Hb1Ac of 8.8%. Common adverse reaction in T1DM patients treated with Afrezza shows that cough (27%) is significantly higher in Afrezza treated individual than comparator (5.2%). Cough

was also the most common cause for discontinuation in Afrezza treated group. Severe hypoglycemia (5.1%) and non-severe hypoglycemia (67%) are higher in Afrezza group compared to 1.7% and 30% in placebo-treated individuals. Throat pain increased from 1.9% (subcutaneous insulin) to 5.5% (Afrezza) in T1DM and pulmonary function tests decreased significantly 5.5% (Afrezza) compared to 1.0% (subcutaneous insulin) in T1DM patients. Afrezza has not been studied in patients younger than 18 years of age. Frequent glucose monitoring and dose adjustments may be necessary for Afrezza in patients with renal impairment.

ADVERSE EFFECTS

Hypoglycemia is the most common adverse reaction with insulin including Afrezza. Severe hypoglycemia can cause seizures and potentially fatal. Individuals and health care providers must be educated to recognize and treat hypoglycemia. Excess Afrezza administration may cause hypoglycemia and hypokalemia. Severe episodes of hypoglycemia with coma, seizures and neurological impairment may be treated with an intramuscular injection of glucagon or concentrated intravenous glucose. Hypokalemia is to be treated appropriately.

Afrezza causes a decline in lung function over time as measured by forced expiratory volume 1 sec (FEV1). Consider discontinuing Afrezza in individuals, who have a decline of ≥20 in FEV1 from baseline.[8] In individual at risk for diabetic ketoacidosis, consider alternate route of insulin administration. Individual treated with Afrezza and peroxisome proliferator activated receptor gamma agonists should be monitored for signs and symptoms of heart failure.

CONTRAINDICATIONS

Afrezza is not recommended for the treatment of diabetic ketoacidosis. It is also contraindicated during episodes of hypoglycemia. Afrezza is contraindicated in patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease. It is not recommended in patients who smoke or have recently stopped smoking. There is a risk of acute bronchospasm in patients with chronic lung disease. Before initiating, prescribers must perform a detailed medical history, physical examination, and spirometry (FEV1) in all patients, to identify potential underlying lung disease. Afrezza is also contraindicated in individual hypersensitive to regular insulin or any of the Afrezza excipients. Afrezza has been not studied in patients younger than 18 years of age.

CONCLUSION

Afrezza provides a novel rapid-acting oral inhalational human insulin therapeutic option in T1DM and T2DM management which is convenient and easy to use. Clinical studies demonstrate glycemic efficacy, reduced hypoglycemia, and weight neutrality. Afrezza's unique pharmacokinetics and pharmacodynamics profile more closely mimics endogenous prandial insulin secretion compared with currently available subcutaneous injection of rapid-acting analogs and RHI.[9] Thus, Afrezza provides an alternative mode of insulin delivery for patients with T1DM/T2DM for whom the subcutaneous injection is a barrier to starting/maintaining insulin therapy and also for those individuals in whom weight and hypoglycemia are significant concern.

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