An Inhaled Insulin (Afrezza)

The FDA has approved an inhaled, rapid-acting, dry-powder formulation of recombinant human insulin (Afrezza – Mannkind/Sanofi) for treatment of adults with type 1 or type 2 diabetes. In patients with type 1 diabetes, the drug must be used in combination with long-acting insulin. Another inhaled, rapid-acting insulin (Exubera) was approved in 2006 for the same indication, but was withdrawn from the market the following year.1

Pronunciation Key
Afrezza: uh frezz’ uh

RAPID-ACTING INSULINS – Rapid-acting insulin analogs have a faster onset and shorter duration of action than regular insulin and are generally administered just before, at the start of, or soon after a meal. In addition to being more convenient, these drugs appear to be slightly more effective than regular insulin in decreasing HbA1c, with less hypoglycemia.2 Three rapid-acting insulin analogs are currently available: insulin aspart (Novolog), insulin glulisine (Apidra), and insulin lispro (Humalog). All three are approved for use in both type 1 and type 2 diabetes, either by subcutaneous (SC) injection, insulin pump, or intravenous infusion.

PHARMACOKINETICS – An unpublished pharmacokinetic study (summarized in the package insert) conducted in 12 patients with type 1 diabetes compared 8 units of Afrezza with the same dose of insulin lispro. Serum concentrations peaked earlier with Afrezza, but the onset of action was similar with both drugs. The maximum effect occurred about 50 minutes after administration of Afrezza and about 120 minutes after injection of insulin lispro. Inhaled insulin had a shorter duration of action than insulin lispro (~3 vs. ~4 hours).

CLINICAL STUDIES – Approval of Afrezza was based on 2 unpublished clinical studies which are summarized in the package insert. The first trial randomized 344 adults with uncontrolled type 1 diabetes to mealtime doses of inhaled insulin or SC injections of insulin aspart, both in combination with basal insulin. After 24 weeks, the mean reduction in HbA1c with inhaled insulin was noninferior to the reduction with insulin aspart (-0.21% vs. -0.40%; the prespecified noninferiority margin was 0.4%). The percentage of patients who achieved an HbA1c ≤7% was 27.1% with insulin aspart and 13.8% with inhaled insulin.

The second trial included 479 adults with type 2 diabetes that was inadequately controlled despite treatment with metformin alone or ≥2 oral antidiabetic drugs. Patients were randomized to inhaled insulin or placebo; both groups received stable doses of oral antidiabetic drugs. After 24 weeks, patients using inhaled insulin had a significantly greater mean reduction in HbA1c than those on placebo (-0.82% vs.

<table>
<thead>
<tr>
<th>Table 1. Rapid-Acting Insulins</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Insulin inhalation powder – Afrezza (Mannkind/Sanofi)</td>
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<tr>
<td>Insulin aspart – Novolog (Novo Nordisk)</td>
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<td>Insulin glulisine – Apidra (Sanofi)</td>
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<td>Insulin lispro – Humalog (Lilly)</td>
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* FDA pregnancy categories: B = no evidence of risk in humans; C = risk cannot be ruled out
1. Approximate wholesale acquisition cost (WAC) for 25 days of 24 units daily of mealtime insulin. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy.
2. Administered via inhaler.
3. Prefilled, disposable pen.
4. Cost for one package containing 60 8-unit and 30 4-unit cartridges of Afrezza and 2 inhalers.
5. Cost for 2 pens.
-0.42%) and the percentage of patients who achieved an HbA1c ≤7% was 32.2% with inhaled insulin and 15.3% with placebo.

A 52-week, open-label trial enrolled 677 patients with type 2 diabetes that was inadequately controlled despite insulin therapy with or without oral antidiabetic drugs; patients were randomized to receive inhaled insulin plus bedtime insulin glargine or twice-daily biaspart insulin, a premixed SC insulin containing 70% insulin aspart protamine suspension (similar to NPH insulin) and 30% insulin aspart. The mean reduction in HbA1c in the inhaled insulin group was noninferior to that in the biaspart insulin group (-0.68% vs -0.76%).

ADVERSE EFFECTS — The most common adverse effects of Afrezza have been throat pain or irritation, cough, and hypoglycemia. Cough occurred in about 27% of patients who received inhaled insulin, and was the most common reason for discontinuing the drug. In patients with type 2 diabetes, severe and non-severe hypoglycemia were more common in patients who took Afrezza (5.1% and 67% vs. 1.7% and 30% with placebo).

Clinical trials of Afrezza lasting up to 2 years found that forced expiratory volume in one second (FEV1) declined by 40 mL more among patients using inhaled insulin than in patients on other antidiabetic drugs. The reduction occurred within the first 3 months of treatment and persisted for 2 years. Pulmonary function should be assessed before starting and 6 months after starting treatment, and then annually thereafter; more frequent monitoring may be necessary in patients who exhibit pulmonary symptoms such as wheezing, bronchospasm, breathing difficulties, or cough. If FEV1 declines by ≥20% or if pulmonary symptoms persist, Afrezza should be stopped.

In clinical trials, lung cancer was observed in 2 patients with a history of heavy tobacco use taking Afrezza, and in no patients using comparators. After trial completion, 2 additional cases of lung cancer were reported in non-smokers who had taken Afrezza. The FDA is requiring the manufacturer to conduct a 5-year clinical trial to assess long-term malignancy risk.

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Diabetic ketoacidosis was more common in patients with type 1 diabetes who took Afrezza than in those who received insulin comparators (0.43% vs. 0.14%).

DOSAGE AND ADMINISTRATION — Afrezza is packaged in blue or green cartridges providing 4 or 8 units of insulin, respectively. The drug is administered in a single inhalation from a palm-sized, breath-powered, dry-powder inhaler device. Multiple inhalations are needed for doses greater than 8 units because only one cartridge can be used per inhalation. The inhaler must be replaced after 15 days.

Afrezza is taken at the beginning of a meal. Insulin-naive patients should start with 4 units per meal. For patients switching from SC insulin, their current dose should be rounded up to the nearest multiple of 4 to arrive at the equivalent dose of inhaled insulin. For example, 4, 6, and 9 units of SC insulin would be converted to 4, 8, and 12 units of Afrezza.

Patients switching from pre-mixed insulin should divide half their current dose among 3 daily meals, then convert each dose to inhaled insulin by rounding up to the nearest multiple of 4. The other half should be given as injected basal insulin.

CONCLUSION — Afrezza, the only inhaled formulation of insulin currently available in the US, appears to be only modestly effective in reducing HbA1c. Cough is a common side effect and the long-term pulmonary safety of inhaling insulin is unknown.
