Drug Use Research & Management Program
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New Drug Evaluation: (insulin human) inhalation powder

Month/Year of Review: September 2014
End date of literature search: July 2014
Generic Name: (insulin human) inhalation powder
Brand Name (Manufacturer): Afrezza® (MannKind Corporation)

FDA Approved Indication: Insulin inahalation powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use include:

- In patients with type 1 diabetes (T1DM), must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke

Research Questions:

- Is insulin human inhalation powder (IHIP) safe and effective in improving glycemic control in patients with T1DMt and type 2 diabetes mellitus(T2DM)?
- How does IHIP differ from currently available insulin products?
- Are there certain patient subgroups that benefit from the use of IHIP?

Conclusions:

- There is low quality evidence to show that IHIP is non-inferior to insulin aspart for reducing HbA1c in patients with T1DM. Pivotal trials remain unpublished, but data from FDA briefing documents indicate that IHIP performed statistically worse than insulin aspart despite falling within non-inferiority margins.
- There is moderate quality evidence to show that IHIP is effective at reducing HbA1c in patients with type 2 diabetes. Only one phase 3 trial, of at least six months duration is published, and it shows that reductions in HbA1c are comparable between IHIP + glargine and NovoLog Mix 70/30.
- There are two unpublished phase 3 trials in which the primary endpoint was not met when compared to insulin aspart (in combination with insulin glargine) or when compared to sulfonylureas (in combination with metformin). There is one unpublished phase 3 trial in which IHIP was superior to placebo. As these trials are unpublished, the quality of the evidence cannot be assessed and results should be interpreted with caution.
- There is no evidence to show that IHIP results in an improved quality of life when compared to an active treatment alternative. One phase 3 trial evaluated quality of life as a secondary endpoint and found no difference compared to injectable insulin.

- The most common adverse events associated with IHIP were hypoglycemia, cough, and throat pain or irritation. Pulmonary adverse effects were similar in patients treated with IHIP versus placebo. A two year study shows that there is a decline in pulmonary function tests after treatment with IHIP, but it is minimal and not clinically significant.
- As this is a new route of administration, pulmonary toxicity remains a concern. The FDA has requested several post-marketing studies, including a clinical trial that evaluates the potential risk for pulmonary malignancy, cardiovascular events, and long-term effects on pulmonary function.
- Long term efficacy and safety data is necessary to better define the role of IHIP in the treatment of patients with T1DM and T2DM.

Recommendations:

- Due to low-moderate quality data in type 1 and type 2 diabetes, and a lack of long term efficacy and safety data, IHIP should be a non-preferred agent on the PDL. There is no evidence to show it offers any advantages in efficacy or safety when compared to injectable insulin products for which long term data is available.
- Once agent is available on the market, monitor for inappropriate use.

Background:

There were over 29 million people in the United States in 2012 who had diabetes, which was 9.3% of the population.[1] About 90% of individuals with diabetes worldwide have type 2 diabetes mellitus, although many remain undiagnosed.[2] Diabetes was the seventh leading cause of death in the United States in 2010.[2] People with diabetes are 1.7 times more likely to die of cardiovascular disease, 1.8 times more likely to have a heart attack, and 1.5 times more likely to have a stroke.[1] Diabetes is also associated with microvascular disease leading to increased kidney disease, eye problems, and amputations.[1]

There are two classes of medications (insulin and amylin agonists) approved for the treatment of patients with T1DM and 12 classes (insulin inclusive) of drugs approved for the treatment of T2DM in the United States.[2] All FDA approved insulins, besides Afrezza, are delivered via the subcutaneous route (SC) in multiple daily injections or via an insulin pump device; regular insulin can be given intravenously for short periods in the hospital setting. The current SC insulins vary in their duration of action, ranging from short to long acting. For patients in whom endogenous insulin is insufficient or not present, therapy is aimed at imitating the pattern of endogenous insulin secretion (e.g., basal to meal time ratio of 50:50 often time administered as one basal and three meal time injections).[2] The American Diabetes Association recommends lowering HbA1c to below or around 7% for most nonpregnant adults. More stringent goals may be considered for some patients, depending on comorbidities and response to current therapy.[2]

The first inhaled insulin product, Exubera, was approved by the FDA in 2006, but was withdrawn from the market one year later due to concerns of lung cancer and a lack of acceptance by patients and prescribers. The Exubera inhaler was administered using a large device with low portability and it was difficult to train patients and providers on proper use.[3] The MannKind Corporation continued to develop an inhaled form of insulin, Afrezza, which was approved by the FDA in 2014.

Afrezza is a drug-device combination that consists of single-use cartridges of a dry powder formulation of recombinant regular human insulin (also referred to as technosphere insulin), and a breath-activated inhaler. Afrezza is a rapid-acting insulin that is intended to cover meal time insulin requirements for patients with

T1DM and T2DM.[2] The Technosphere Technology platform, developed by the MannKind Corporation, is a new method for pulmonary delivery of medications, which allows proteins, like insulin, to be administered by inhalation. The Technosphere inhalation platform is made possible by the development of an excipient called fumaryl diketopiperazine (FDKP), which is an inert, small molecule. FDKP forms the particle matrix that delivers the active pharmaceutical ingredient to the lungs.[4]

IHIP is administered using the DreamBoat inhaler, a thumb-sized inhalation device patented by MannKind. To use a DreamBoat inhaler, patients must load the cartridge, close the device, and inhale. The inhalers are also disposable, eliminating the need to wash and dry the device, but inhalers should be discarded and replaced with a new inhaler after 15 days of use. Cartridges are available in 2 different strengths, 4 units and 8 units, so patients using higher doses of mealtime insulin (>8 units), will have to use multiple cartridges per meal. Pharmacokinetic studies show that IHIP has a more rapid absorption and elimination than subcutaneously administered regular human insulin, reaching maximum serum insulin concentrations 12-15 minutes after administration compared to 120 minutes for regular human insulin (Rave, Prescribing info).[5,6]

Clinical Efficacy:

IHIP has a complex regulatory history. Throughout the course of development, two different inhalers were used to administer IHIP, each developed by MannKind Corporation. The MedTone inhaler was the first inhaler developed and used in clinical trials. After the initial trials were completed, MannKind developed the DreamBoat inhaler (also known as the Gen2 inhaler), which is the commercially available device that was brought to market with IHIP. When MannKind initially submitted for FDA approval in 2009, the Agency required additional clinical trials, with at least one that included a head to head comparison of MedTone and DreamBoat inhalers with regards to pulmonary safety.[7]

Studies completed using the MedTone inhaler

In total, there were three phase 4 trials of at least 6 months duration that evaluated IHIP using the MedTone inhaler, one of which is published. One trial evaluated patients with T1DM (study 009) and three studies were completed in T2DM.

The published Phase 3 trial evaluated the efficacy and safety of IHIP in combination with insulin glargine and compared it to that of twice daily biaspart insulin (NovoLog Mix 70/30). Patients included in the trial had T2DM, a HbA1c between 7-11%, and were previously treated with insulin (with or without oral agents). Patients using metformin or sulfonylureas in combination with insulin were allowed to remain on oral therapy throughout the trial, and concomitant use was similar across both treatment groups. Chronic pulmonary disease and unstable diabetes are among several excluded conditions. Unstable diabetes was defined as ≥2 episodes of severe hypoglycemia, or any admission to hospital or visit to an emergency department for diabetes within the preceding 6 months.[8]

This study found that IHIP was non-inferior to biaspart insulin for the primary endpoint of change in HbA1c from baseline to 52 weeks. This was true for all analyzed populations, including the per protocol and intent-to-treat populations [IHIP: -0.59% (95% CI -0.71, -0.47); biaspart: -0.71% (95% CI -0.83, -0.59), difference: 0.12% (95% CI -0.05, 0.29), modified intent-to-treat]. The change in fasting plasma glucose over 52 weeks was measured as a secondary endpoint, and was greater for IHIP (2mmol/L) than for biaspart insulin (1mmol/L), with a difference of 1mmol/L [p=0.0029 (95% CI -1.6, -0.3)]. IHIP and biaspart insulins performed similarly for remaining secondary endpoints, including postprandial glucose AUC, and proportion of patients with HbA1c of ≤7%.[8]

Investigators evaluated quality of life using the SF-36 Quality of Life (QoL) instrument and the insulin treatment questionnaire, as additional secondary endpoints. While there were significant differences from baseline in each treatment group, there was no difference between the two treatment groups for

decrease in diabetes worries (p=0.1825), attitudes towards insulin therapy/treatment satisfaction/treatment preference (p=0.5276). This study showed that IHIP could reduce and maintain improvements HbA1c compared to biaspart insulin, but it was not compared to a basal-bolus insulin regimen, which is commonly used in patients with diabetes, and lack of a glargine-only arm may have confounded results. Additionally, due to the differences in administration and variable dosing of study drugs, study participants were not blinded.[2,8]

Of the studies initially submitted for FDA approval, this study was the only one to meet the primary endpoint. The other studies remain unpublished, but additional details were available in the FDA briefing document.

Study 014 was an open-label, 24 week trial comparing IHIP + glargine to insulin aspart (SQ) + glargine in patients with T2DM, in Russia. Roughly 80% and 97% of IHIP and SC patients completed the study, respectively, with adverse events being the primary reason for discontinuation. According to the FDA briefing document, the two treatment groups were not comparable when using the intent-to-treat population with last observation carried forward, so the sponsor conducted the analysis on the intent-to-treat population without the last-observation-carried forward, which potentially biased the results. The FDA reviewer also noted that IHIP was statistically inferior to SC insulin because the upper-bound of the 95% confidence interval was 0.6%, which is above the pre-specified non-inferiority margin of 0.4% and the lower bound of the 95% confidence interval for the HbA1c treatment difference for the intent-to-treat population using last-observation-carried-forward was 0.1%.[2]

Study 103 was another open-label trial completed in patients with T2DM and compared IHIP vs. IHIP + metformin vs. metformin + sulfonylurea. Patients in the study had HbA1c 7.5-11% and were on a stable dose of metformin (≥1000 mg/day) and at least half the maximum recommended dose of an insulin secretagogue (either sulfonylurea or glinide). The trial found that IHIP + metformin was not superior to the sulfonylrea + metformin. The mean reduction from baseline in HbA1c was -0.7% in the IHIP + metformin group compared to -0.8% in the sulfonylurea + metformin group (p=0.51). The FDA reviewer identified several limitations with the trial design as the treatment duration was too short and inconsistent metformin doses were used among the different treatment groups. Lastly, investigators compared an add-on therapy to continuation therapy which could potentially overestimate the true effect of the medication.[2]

Study 009 was an open-label trial comparing IHIP + glargine to insulin aspart (SC) + glargine in patients with T1DM and HbA1c 7-11% (n=539). Insulin dose titration was permitted throughout the study and the dose of IHIP was based on a conversion of 15 units IHIP for every 5 units of SC insulin, with a max dose of 90 units with meals. There was a high dropout rate during the trial with 66% and 76% of patients in the IHIP and SC groups, respectively, completing the trial. Reasons for drop out were primarily due to lack of efficacy (hyperglycemia, increase blood glucose), which occurred in 7.6% of IHIP-treated patients and 0.7% of SC treated patients. After 52 weeks, IHIP was found to be inferior to SC insulin with a treatment difference in mean change in HbA1c of 0.2% (95%CI 0.1, 0.404), similar to study 014. FDA reviewers indicate that there was minimal titration of insulin during this study and it is possible the treatment difference between the two regimens may be more pronounced if treatments were titrated differently.[2]

Studies completed using the DreamBoat (Gen2) inhaler

In an effort to meet the FDA's request for additional information, two Phase 3 trials were completed using the DreamBoat inhaler, one in patients with T1DM (Study 171) and one in patients with T2DM (Study 175). Both trials titrated patients on IHIP using a dose conversion of 10 units IHIP for every 4 units of rapid acting insulin analog, which was different than the dose conversion used when the MedTone inhaler was studied. Study 171 titrated doses based on 90-minute postprandial blood glucose values, and study 171 titrated doses based on blood glucose values prior to the next meal. Both trials were randomized, multicenter trials, although study 171 was open-label, while study 175 was placebo-controlled.

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Study 171 (n=518), completed in patients with T1DM and HbA1c ≥7.5% and ≤10%, evaluated the efficacy of IHIP + basal insulin versus insulin aspart + basal insulin, and the effects on pulmonary safety between the DreamBoat and MedTone inhalers. Patients were randomized to one of three treatment groups: SC insulin (SC), IHIP administered using the DreamBoat inhaler (IHIP-DB), or IHIP administered using the MedTone inhaler (IHIP-MT); each treatment arm received basal insulin. After 24 weeks, the mean reduction in HbA1c from baseline was -0.21% for patients treated with IHIP-DB and -0.4% for patients treated with SC insulin, for a treatment difference of 0.19% (95% CI 0.02-0.36). Efficacy results were not reported for patients in the IHIP-MT group, as this data was used only to assess safety endpoints for each of the inhalers. Non-inferiority was met, as the upper bound of the 95% CI was lower than the prespecified margin of 0.4%, however IHIP performed statistically worse than insulin aspart. Additionally, more patients treated with insulin aspart achieved HbA1c ≤ 7% at the end of the trial (30.7% vs 18.3%, p=0.0158).[2]

Study 175 (n=353), completed in patients with T2DM and HbA1c ≥7.5% and ≤10%, evaluated the efficacy of IHIP compared to placebo when added to oral antidiabetic medications in insulin-naïve patients. To be included in the trial, patients had to be on a stable dose of metformin as monotherapy, or at least 2 oral antidiabetic medications. After 24 weeks, investigators found that patients receiving IHIP + background therapy experienced a greater reduction in HbA1c (-0.82%) compared to those receiving placebo + background therapy (-0.42%) for a treatment difference of -0.4% (95% CI -0.57, -0.23), p<0.0001). More patients treated with IHIP achieved HbA1c ≤ 7% at the end of the trial, than with placebo (37.7% vs 19%, p=0.0005).[2]

Clinical Safety:

In the Rosenstock et al trial, safety was assessed in all patients who received at least one dose of the study drug. Adverse events occurred in 85% of patients using IHIP and 89% of those using SC insulin. Hypoglycemia was the most commonly reported treatment-related adverse event, occurring in 31% of patients on IHIP and 49% of patients on subcutaneous insulin. The rate of mild to moderate hypoglycemia per patient months was significantly lower in patients who received IHIP (p=0.0029), but the difference in event rate of severe hypoglycemia was not significantly different (p=0.0591). Cough was commonly reported in the IHIP group (32% vs 4% in the subcutaneous group), and most cases occurred within 10 minutes of inhalation. Changes in pulmonary function tests were similar between treatment groups. More patients in the IHIP group discontinued treatment due to adverse events (9% vs 4%), primarily due to adverse events affecting the respiratory tract.[8]

In the FDA review, information from all submitted clinical trials was pooled, analyzed, and reported. Death rates in clinical trials were low, and appeared to be unrelated to treatment with IHIP. In total 0.4% of IHIP-treated patients died (9/2409). The rate of patients dropping out due to adverse events was higher in patients treated with IHIP compared to other groups, with adverse events related to cough or pulmonary effects and lack of efficacy being the most common reasons for discontinuation. The cumulative incidence of discontinuations due to adverse events was 6.9% for IHIP and 0.6% for comparator groups. These rates are also similar when comparing patients using the DreamBoat inhaler for administration (7.3%) to those using the MedTone inhaler for administration (6.2%). Although the discontinuation rate was higher with the DreamBoat inhaler, the FDA did not feel that the difference was substantial enough to be clinically meaningful. Although four IHIP-treated patients developed malignancy, there is still an unclear association with IHIP and cancer. The most common adverse event was cough, with an incidence of 30%, and this typically occurred within 10 minutes and tended to decrease over time.[2]

Pulmonary adverse effects are a concern with inhaled insulin and were evaluated in a randomized, open-label, two-year study. In total, 1,699 patients with T1DM or T2DM were randomized to prandial IHIP or a usual care regimen without IHIP for 24 months. Investigators also enrolled a cohort of individuals without diabetes to examine changes in lung function over two years. Baseline lung function was comparable across all three treatment groups. After two years, a small decline from baseline FEV_1 was seen in all three groups, with the smallest change in the group without diabetes. IHIP was non-inferior to usual care for mean

Forced Expiratory Volume in 1 second (FEV_1) change from baseline (mean treatment group difference was 0.037, 95% CI 0.014 to0.060). There was an early decline in pulmonary function tests noted after month 3, but after the initial decline, the annual rates of decline in FEV_1, Forced Vital Capacity (FVC), and Diffusing Lung Capacity (DLco) from months 3-24 were not statistically different between groups, indicating that Pulmonary Function Test (PFT) changes associated with IHIP were non-progressive for up to two years.[9]

While the prior study evaluated the effects of IHIP administered using the MedTone inhaler, the FDA briefing document compared lung function of patients using IHIP administered via the MedTone versus DreamBoat inhalers. In patients with T1DM, there was no significant difference in the mean change from baseline in FEV1 between the DreamBoat and MedTone inhaler groups [difference=0.01L (95%CI 09.02, 0.04)]. In patients with T2DM, the change in FEV1 from baseline was similar to that of the MedTone inhaler in the original submission to the FDA (-0.13 L for the DreamBoat and the MedTone inhaler). Coughing was commonly reported, with similar rates occurring in patients using the DreamBoat and MedTone inhalers (incidence of cough using DreamBoat inhaler: 32% in T1DM, 24% in T2DM vs 2% in insulin aspart vs 20% with placebo]. Patients with asthma, COPD, or other underlying lung disease were excluded from clinical trials and IHIP should not be used in these patients. The FDA is requiring postmarketing studies to evaluate efficacy and safety in pediatric patients, the risk of pulmonary malignancy, and to further refine the pharmacokinetic profile of IHIP.[2]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Morbidity
3) Difference in mean change in HbA1c from baseline

Primary Study Endpoint:

1) Difference in mean change in HbA1c from baseline

Ref./Study Design	Drug Regimens/ Duration	Patient Population	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

Rosenstock et al. 2010[9] R, OL, PG 52 weeks	1. inhaled human insulin powder + insulin glargine (IHIP) (n= 302) *~50% of total daily insulin dose was given as basal insulin. The remainder was given as inhaled insulin, adjusted in 15U increments, max 90 U per meal* 2. Subcutaneous biaspart insulin (SCI) (n=316) *Premixed, 70% insulin aspart protamine suspension and 30% insulin asapart (rDNA origin)*	Demographics (IHIP, SC): • Age: 55.9, 55.9 • Weight (kg): 88.3, 85.8 • BMI (kg/m^2):31.6, 31.1 • HbA1c: 8.7%, 8.7% • Fasting plasma glucose (mmol/L): 9.4, 9.8 • Duration of diabetes (years): 13, 13.7 Inclusion Criteria: • Age 18-80 • Type 2 diabetes • HbA1c 7-11% • Non-smoking for ≥6 months prior • FEV_1 and DL_{CO} ≥ 70% of predicted • Total lung capacity ≥ 80% of predicted • BMI ≤ 40kg/m^2 • Required < 1.4IU insulin/kg Exclusion Criteria: • Clinical significant diabetes complication • Hepatic or renal disease • Current drug or alcohol abuse • Severe or several allergies • Chronic pulmonary disease • Major psychiatric disorders • Unstable diabetes	Δ in HbA1c at 52 weeks *(modified ITT, LOCF):* IHIP: -0.59% SCI: -0.71% Pbo: 54.9% Difference: 0.12% (95%CI -0.05, 0.29) Δ in HbA1c at 52 weeks *(per protocol):* IHIP: -0.68% SCI: -0.76% Pbo: 54.9% Difference: 0.07% (95%CI -0.13, 0.27)	N/A	Treatment withdrawal*:* IHIP: 32% SCI: 24% Withdrawal due to adverse events*:* IHIP: 9% SCI: 4%	N/A	**Quality Rating: Fair** **Internal Validity:** Selection: Adequate randomization assignment (computer interactive voice response); groups similar at baseline. Performance: This was an unblinded study using two different routes of administration. Detection: Unclear if outcome assessors were blinded. Attrition: 7 of the 334 patients randomized to IHIP were lost to follow-up. 22 of the 343 patients randomized to subcutaneous insulin were lost to follow-up **External Validity:** Recruitment: This is a multicenter study that recruited patients from hospitals and clinics in Argentina, Brazil, Canada, Chile, Mexico, Poland, Russia, Spain, UK, and USA Patient Characteristics: Adult patients with type 2 diabetes moderately uncontrolled on insulin therapy without comorbidities Setting: Patients received care at hospitals or outpatient clinics. Outcomes: Primary endpoint (change in HbA1c), and secondary endpoints were measured after 52 weeks Change in HbA1c is an appropriate surrogate outcome for this study. No health outcomes, such as mortality, were studied..
R: randomized, OL: open-label, PG: parallel group, FEV_1: Forced expiratory volume in 1 second, DL_{CO}: diffusing lung capacity, BMI: body mass index, ITT: intention-to-treat, LOCF: last observation carried forward							

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Appendix 1: Specific Drug Information

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CLINICAL PHARMACOLOGY

PHARMACOKINETICS[6]

Parameter	Result
Time to maximum serum concentration	12-15 minutes
Duration of action	160-180 minutes
Half-Life	28-39 minutes
Metabolism	Phase I and II reactions in hepatocytes

- Based on inhaled Afrezza 4-32 units in 12 type 1 diabetes patients

This inhaled insulin has a lower bioavailability compared to subcutaneous insulin. The relative bioavailability is 20-30% that of subcutaneous insulin. The studies accounted for this lower bioavailability in the pivotal trials using the following dose alogorithm (10 units of Afrezza for 4 units of SC insulin).[6]

DOSE & AVAILABILITY[6]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
4 and 8 unit cartridges	Inhaled	With meals	Varies by patient	Monitor blood sugars closely, may cause hypoglycemia. Dose reduction may be required.	Monitor blood sugars closely, may cause hypoglycemia. Dose reduction may be required.	Not been studied in patients younger than 18 years of age	No overall differences in safety or effectiveness were observed in trials.	Must be use the IHIP inhaler to administer the doses

DRUG SAFETY[6]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning: Risk of acute bronchospasm in patients with chronic lung disease.

Contraindications: During episodes of hypoglycemia; chronic lung disease, such as asthma, or chronic obstructive pulmonary disease; hypersensitivity to regular human insulin or any of the excipients

Warnings and Precautions:

- Acute bronchospasm- Observed in patients with asthma and COPD.
- Change in insulin regimen- carry out under close medical supervision

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- Hypoglycemia- May be life-threatening. Monitor glucose more frequently when making changes to insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity, and in patients with renal or hepatic impairment.
- Decline in pulmonary function- Assess pulmonary function before initiating, after 6 months of therapy, and annually
- Lung cancer- Do not use in the setting of active lung cancer
- Diabetic ketoacidosis- More patients experienced diabetic ketoacidosis in clinical trials.
- Hypersensitivity reactions- Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products.
- Hypokalemia- May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated.
- Fluid Retention and heart failure with concomitant use with thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.

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