Canadian Agency for Drugs and Technologies in Health

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Afrezza Inhaled Insulin for Diabetes Mellitus

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Summary

- ✓ **Afrezza is a drug-device combination consisting of Technosphere insulin (TI) inhalation powder and a product-specific breath-activated inhaler.[1] TI cartridges are used with an inhaler one minute before eating for managing type 1 and type 2 diabetes.**
- ✓ **TI significantly reduces postprandial glucose and glycated hemoglobin (A1C) levels in type 2 diabetes patients taking oral antidiabetic drugs or concurrent insulin glargine (IG) compared with placebo. Patients with poorly controlled type 2 diabetes taking TI showed comparable reductions in postprandial glucose and A1C compared with biaspart insulin (BI) recipients.**
- ✓ **No significant differences in hypoglycemia, cough, pulmonary function, or weight were reported between patients receiving TI compared with placebo.[2,3] Compared with BI, patients taking TI plus IG experienced less weight gain and hypoglycemia but more cough and upper respiratory tract infections.An asymptomatic decline in pulmonary function that was not considered to be clinically significant was observed in both groups but no statistically significant differences in pulmonary function between groups were found.[4]**
- ✓ **To better determine the role of TI in diabetes management, long-term evidence is needed regarding the efficacy of TI compared with rapid-acting prandial insulins in patients with type 1 and type 2 diabetes.**
- ✓ **Afrezza does not currently have Health Canada or European Medicines Agency approval for marketing. Following the removal of the first inhaled insulin Exubera from the market due to lack of acceptance by patients and physicians, acceptance of Afrezza by patients and physicians is a critical factor affecting diffusion if regulatory approval is obtained.**

Background

Since the discovery of insulin in 1921, subcutaneous injection remains a limitation to insulin use because of patient compliance. Thus, other delivery systems have been under investigation.[5] The first inhaled insulin Exubera (human insulin [recombinant DNA origin]; Pfizer collaboration with Nektar Therapeutics, San Carlos, California, USA) was approved for use by the US Food and Drug Administration (FDA) in 2006. However, Pfizer ceased manufacturing Exubera in 2007 due to lack of acceptance by patients and physicians, and possible lung cancer concerns.[1] The Exubera inhaler was reported to be big and clumsy to use, and adequate training of patients and health care providers on its use was difficult.[1] While most companies terminated product development after Exubera was removed from the market, MannKind Corporation continued developing inhaled insulin.

The Technology

Afrezza (human insulin [recombinant DNA origin]; (MannKind Corporation, Valencia, California, USA) is a drug-device combination consisting of pre-metered, single-use cartridges of TI inhalation powder and a product-specific, breath-activated inhaler.[1] First-generation MedTone inhalers were palm-sized, but thumb-sized second-generation DreamBoat inhalers will be used for the marketing of Afrezza.[5] TI is formed when regular human insulin (RHI) is microencapsulated within fumaryl diketopiperazine and lyophilized for inhalation.[5] Upon inhalation, the microspheres dissolve in the neutral pH of the lungs. TI reaches maximal blood concentrations within 15 minutes of inhalation, with a relative bioavailability of 37% compared to subcutaneous RHI, and a half-life of 45 minutes, which is much less than subcutaneous regular insulin (approximately 284 minutes).[5]

Regulatory Status

Afrezza does not currently have Health Canada or European Medicines Agency approval for marketing. The US FDA is reviewing it for use as an inhaled mealtime insulin for managing hyperglycemia in

patients with type 1 and type 2 diabetes mellitus.[5] While MannKind submitted a new drug application in May 2009 based on first-generation MedTone inhaler trials, the FDA requested at least two more comparison trials with the second-generation DreamBoat inhalers. One trial will compare type 1 diabetes patients randomized to TI, placebo, or injected rapid-acting insulin, with or without oral antidiabetic drugs. A second trial will compare poorly controlled type 2 diabetes patients randomized to TI or placebo.

Patient Group

Diabetes — which affects approximately 2.4 million Canadians — occurs when the body is unable to produce or use insulin, resulting in high blood glucose. Long-term high blood glucose levels cause heart disease, stroke, kidney failure, blindness, and nerve damage.[6] Approximately 10% of patients with diabetes have type 1 diabetes, which occurs when the pancreas is no longer able to produce insulin, requiring patients to have insulin injections. Approximately 90% of patients with diabetes have type 2 diabetes, resulting in insulin resistance that is sometimes controlled by lifestyle modification and diet, but that may require medication.[6] Diabetes is diagnosed based on a fasting blood glucose level of ≥ 7 mmol/L (126 mg/dL); two-hour blood glucose of ≥ 11 mmol/L (198 mg/dL) in an oral glucose test; a casual blood glucose level of ≥ 11 mmol/L (198 mg/dL), with increased urination, hunger and thirst; or an A1C ≥ 6.5%.[6] Approximately 6.8% of Canadians have diabetes, but 20% of cases remain undiagnosed.[6]

Current Practice

Canadian practice guidelines recommend that type 1 and 2 patients with diabetes reduce their blood glucose levels to prevent long-term complications.[7] Type 1 diabetes is managed with multiple basal and prandial insulin injections per day, matching prandial insulin to blood glucose and activity.[7] Type 2 diabetes is treated with lifestyle changes and metformin (as the first-line oral antidiabetic drug). Because type 2 diabetes is progressive, most patients will have two or more oral antidiabetic drugs added to their regimens and will eventually be prescribed insulin.[8]

The Evidence

Although five phase 2 and six phase 3 trials evaluate TI for diabetes, few are published in full, hindering critical appraisal. Published phase 2[2,3] and 3[4] studies have involved a total of 1,027 patients from at least 14 countries and include a dose-response study[2] and two studies comparing the efficacy and safety of TI[3] or TI with IG[4] versus Technosphere placebo powder (TP)[3] or BI (Table 1).[4] Published studies included type 2 diabetes patients ranging in age from 56 years to 59 years, A1C levels ranging from 7.0% to11%, and pulmonary function > 70 L/second. These studies followed patients for 11[2] weeks to 52[4] weeks and thus provide limited information about long-term efficacy and risk of weight gain and hypoglycemia. Quality of life and treatment satisfaction were similar among groups.[9,10] To better determine the role of TI in diabetes management, long-term evidence is needed on how TI compares with rapid-acting prandial insulins in patients with type 1 and type 2 diabetes.

A phase 2 dose-response, double-blinded randomized controlled trial (RCT) compared four doses of TI plus IG versus TP plus IG given to 227 patients with type 2 diabetes for 11 weeks.[2] The TI group had statistically significant dose-dependent reductions in A1C compared to baseline (–0.4, –0.5, –0.5, and –0.6% for the 14, 28, 42, and 56 unit TI doses, respectively; $P \leq 0.05$ overall) and to TP (–0.4, –0.7, –0.7, and –0.8% for the 14, 28, 42, and 56 unit doses, respectively; $P < 0.04$ for all).[2] Postprandial glucose was significantly reduced in all but one TI group (–28, –41, and –40 mg/dL for 28, 42, and 56 units TI, respectively; $P < 0.001$ overall).[2] The lack of apparent effect on postprandial excursion (the change in glucose concentration before and after a meal) in this group may be the result of the relatively low-calorie (360 kcal, 45 gram carbohydrate) meal consumed by patients in the study. In summation, TI plus IG demonstrated dose-dependent reductions in postprandial glucose and A1C.

Another phase 2 double-blinded RCT compared 126 insulin-naive type 2 diabetes patients to TI or TP.[3] TI or TP was titrated to postprandial glucose for 12 weeks while patients maintained their oral antidiabetic drugs.[3] TI reduced A1C from baseline significantly more than TP (–0.7% versus –0.3%, $P = 0.003$).[3] TI significantly reduced postprandial glucose compared with TP (34 versus 60 mg/dL; $P < 0.0001$).[3] In summation, combined with oral antidiabetic drugs, TI significantly reduced postprandial glucose and A1C levels.[3]

A phase 3 open-label trial randomized 677 poorly controlled type 2 diabetes patients to TI or BI, with or without oral hypoglycemic agents, for 52 weeks.[4]

Patients had A1C levels between 7% and 11% despite insulin therapy with or without oral antidiabetic drugs. Patients received prandial TI with subcutaneous IG or twice-daily subcutaneous BI while continuing oral antidiabetic drugs.[4] Patients receiving TI plus IG showed as similar a change in A1C as those using BI (–0.7, standard error [SE] 0.077, 95% confidence interval [CI], –0.83 to –0.53 versus –0.8%, SE 0.71, 95% CI, –0.90 to –0.62).[4] The between-group difference was 0.07% (SE 0.102, 95% CI, –0.13 to 0.27).[4] While the percentage of patients achieving A1C ≤ 7% were similar between groups (22% TI+IG versus 27% BI; $P = 0.279$),[4] TI significantly reduced one-hour postprandial glucose levels compared with BI (–32 versus –18 mg/dL; $P = 0.0029$).[4] In summation, TI was comparable to BI for reducing A1C in patients with type 2 diabetes.[4]

Adverse Effects

No significant differences in hypoglycemia, cough, pulmonary function, or body weight were found between TI plus IG and placebo groups in phase 2 RCTs.[2,3] In a phase 3 trial comparing TI plus IG to BI,[4] patients taking TI plus IG experienced significantly less weight gain (0.9 kg versus 2.5 kg; $P = 0.0002$) and hypoglycemia (48% versus 69%; $P < 0.0001$) than those taking BI. Both mild-to-moderate and total hypoglycemia were significantly lower with TI plus IG than with BI. The severe hypoglycemia event rate during the late night was also lower with TI plus IG.[4] Patients taking TI plus IG experienced more cough (33% versus 6%) and upper respiratory tract infections (12% versus 7%) compared to those taking BI.[4] An asymptomatic decline in pulmonary function as assessed by pulmonary function tests was observed in both groups over the 52 weeks of the study. The magnitude of the decline was numerically larger in the TI plus IG group but no statistically significant differences were found between groups. Changes in pulmonary function for both groups were considered to be small and not clinically relevant by the investigators.

Administration and Cost

TI powder is available in a cartridge for use with an inhaler one minute before eating.[11] Cartridges are pre-metered with 15 or 30 unit doses of insulin for MedTone inhalers. Second-generation DreamBoat inhalers use 10 unit dose cartridges that may reduce device costs and the incidence of cough.[11] Dosing is individually titrated based on blood glucose such that 15 units of TI is equivalent to 3.8 units of subcutaneous RHI.[12]

The manufacturer's price for Afrezza is unavailable because it has not yet been approved in Canada. However, willingness to pay $CAN153.70 (standard deviation [SD] 99.9) for an inhaled insulin — which was significantly more than the typical $CAN50.00 per month for subcutaneous insulin ($P < 0.01$) — was reported by a pharmacoeconomic study.[13]

Concurrent Developments

Other studied alternative routes of insulin delivery include buccal, oral, rectal, ocular, nasal, and transdermal.[14] The buccal spray Oral-lyn (Generex Biotechnology, Toronto, Canada) gained special access authorization by Health Canada in 2008[15] for use in patients with type 1 diabetes who are failing current standard insulin injectables, pens, or pumps.[15] While it is difficult to prevent degradation of insulin in the gastrointestinal tract, absorption enhancers, protease inhibitors, and mucoadhesives enable oral insulin delivery.[14] Although rectal administration overcomes problems with oral administration, it is difficult to regulate the drug release, and patient compliance is of issue.[14] Ocular devices containing insulin, such as Gelfoam, require greater toxicological stability and regulatory work.[14] The effectiveness of nasal insulin is impaired by thick mucous, enzymatic activity, and mucociliary clearance.[14] Transdermal systems avoid gastrointestinal enzymatic degradation, but stability problems, skin irritation, irregular release profiles, and costs limit use.[14]

Rate of Technology Diffusion

Considering Exubera's market removal, a critical factor influencing the diffusion of Afrezza would be its acceptance by patients and physicians.[5] Thus far, patients using TI report improved attitudes toward insulin therapy and high treatment satisfaction based on an insulin treatment questionnaire and health-related quality-of-life assessment.[9,10] In addition to being less invasive, TI may provide advantages through its rapid action and short duration, and by improving glycemic control with minimal weight gain or hypoglycemia.[11] Its cost requirements for handling and need for regular testing of pulmonary function are also important factors that will influence uptake.[5]

Table 1: Clinical Efficacy of TI for T2DM			
Phase 2 and 3 Studies	**Tack et al. 2008[2] (N = 227)**	**Rosenstock et al. 2008[3] (N = 123)**	**Rosenstock et al. 2010[4] N = 677**
Design	P2, RCT, DB, PC, MC, PG		P3, RCT, OL, MC, PG
Inclusion Criteria	T2DM; A1C: 7.0% to 11.0%; FEV_1 > 70		
Intervention	14 U TI + IG (n = 45) 28 U TI + IG (n = 46) 42 U TI + IG (n = 45) 56 U TI + IG (n = 45)	TI (n = 61) dose titrated by PPG	15 or 30 U TI+IG (n = 334)
Comparator	TP + basal IG (n = 46)	TP (n = 62)	BI (n = 343)
Population Completed/ Randomized	N = 227 ≥1 OAD and/or basal IG 210/227	N = 123 Insulin-naive, 1 OAD 107/126	N = 677 OAD continued in study 462/677
Patient Characteristics Male (%) Mean Age (yr) A1C (%) BMI (kg/m^2)	 51 59 ± 9 9.1 ± 1.4 30 ± 3.9	 67 55 ± 10 7.5 ± 1.2 31 ± 3.6	 47 56 ± 10.3 8.7 ± 1.1 31 ± 4.9
Outcome	A1C mean change from BL; PPG		
Duration	11 weeks	12 weeks	52 weeks
Efficacy A1C Mean Change from BL Between Groups (%)	 14U TI: –0.4; *P* = 0.05 28U TI: –0.5; *P* = 0.004 42U TI: –0.5; *P* = 0.002 56U TI: –0.6; *P* = 0.001 TP: 0.2; *P* = 0.098	 TI: –0.7 TP: –0.3; *P* = 0.003	 TI+IG: –0.7 BI: –0.8
PPG mg/dL	14U TI: NR 28U TI: –28; *P* = 0.007 42U TI:–41; *P* < 0.001 56U TI: –40; *P* < 0.001	TI: 34[a] TP: 60[a]; *P* < 0.0001	TI+IG : –32 BI: –18; *P* = 0.0029
Safety Hypoglycemia n (%)	 14 U TI: 11 (6) 28 U TI: 10 (8) 42 U TI: 13 (17) 56 U TI: 15 (38) TP: 9 (4); NSD	 TI: 26 (42) patients TP: 22 (36); NSD	 TI+IG: 155 (48) BI: 228 (69); *P* < 0.0001
Cough n (%)	14 U TI: 10 (6) 28 U TI: 12 (10) 42 U TI: 4 (5) 56 U TI: 6 (15) TP: 10 (5); NSD	TI: 18 (30) TP:17 (27); NSD	TI+IG: 103 (32) BI: 14 (4); NSD
FEV_1 Mean Change from BL (L)	14 U TI: –0.05 28 U TI: –0.04 42 U TI: –0.06 56 U TI: –0.04 TP: –0.09; NSD	TI: –0.04 TP: –0.01; NSD	TI+IG: –0.13 BI: –0.09; NSD
Weight Mean Change from BL (kg)	14 U TI: –0.3 28 U TI: 1.0 42 U TI: 0.7 56 U TI: 0.6 TP: 0.2; NSD	TI: –0.1 TP: –0.9; NSD	TI+IG: 0.9 BI: 2.5; *P* = 0.0002

Table 1: Clinical Efficacy of TI for T2DM			
Phase 2 and 3 Studies	**Tack et al. 2008[2] (N = 227)**	**Rosenstock et al. 2008[3] (N = 123)**	**Rosenstock et al. 2010[4] N = 677**
HRQoL SF-36	NA	NSD[10]	NSD[9]
Limitations Possible Bias	Publication bias: unpublished studies Selection bias: excluded COPD, renal disease;[2-4] TP > BMI (P = 0.014)[3] Treatment bias: randomization method NR;[2] randomized to fixed dose TI+IG;[2] PG group did not receive IG;[2] TP not conventional insulin[3] Information bias: varying administration times reveal drug, open-label[4] Duration: insufficient[2-4] Industry-funded[2-4] Lack T1DM, comparison with rapid-acting prandial insulin		

A1C = glycated hemoglobin; BI= biaspart insulin; BL = baseline; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; IG = insulin glargine; MC = multicentre; NA = not applicable; NR = not reported; NSD = no significant difference; OAD = oral antidiabetic drug; OL = open label; P2 = phase 2; P3 = phase 3; PC = placebo-controlled; PG = parallel group; PPG = postprandial glucose; RCT = randomized controlled trial; sc = subcutaneous; SF-36 = short-form health survey; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TI = Technosphere insulin; TP = Technosphere placebo; U = units; yr = year.
[a]Baseline-corrected postprandial maximal concentration values compared with placebo.

Implementation Issues

TI mimics physiological insulin release, and is a treatment option for type 1 and type 2 diabetes patients.[1] The DreamBoat device is small, compact, and easy to use, store, and carry. It will require appropriate training by patients and health care professionals. The absorption of TI is not significantly altered in patients who smoke or have chronic obstructive pulmonary disease.[11] Long-term monitoring is required to better understand the adverse effects and impact on patient outcomes.

Updates to this Report

This report was originally published in January 2013. The current update consists of changes to the Adverse Effects section.

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