



Will an Inhaled Insulin Product Reemerge on the Market?

MannKind Corp is hoping its inhaled insulin product , Afrezza® will win FDA approval. The new drug application (NDA) requesting approval to market Afrezza® was accepted by the FDA in May 2009. Several presentations regarding Afrezza® were featured at the American Diabetes Association (ADA) 70th Scientific Sessions, from June 25-29.

Afrezza® (insulin human [rDNA origin]) inhalation powder provides a novel, ultra rapid acting mealtime insulin therapy. It is being studied for use in adult patients with type 1 and type 2 diabetes for the treatment of hyperglycemia. It is a drug-device combination product, consisting of Afrezza® Inhalation Powder pre-metered into single



use dose cartridges and the Afrezza® Inhaler.

A joint ADA-*Lancet* symposium reviewed data showing that Afrezza® has comparable glycemic control versus standard therapy, with less weight gain and less hypoglycemia. It is typically combined with once-daily injected glargine, indicated Daniel Lorber, MD, coauthor of the *Lancet* study.

The study indicated mealtime Afrezza® used with once-daily injected glargine provides equivalent glucose control with fewer injections, less hypoglycemia, and less weight gain than twice-a-day premixed insulin.

A randomized study with 334 patients using Afrezza® and 343 patients using premixed 70/30 insulin twice daily found similar glycemic control results. The Afrezza® group had significantly less weight gain (0.9 kg vs 2.5 kg; $P=.0002$) over the study period. Patients using Afrezza® also had significantly less mild to moderate hypoglycemia (48% vs 69%; $P<.001$) and significantly less severe hypoglycemia (4% vs 10%; $P=.0066$). Pulmonary function test changes from baseline to week 52 were similar in the 2 groups. Exubera®, manufactured by Pfizer, was the first, and so far only, inhaled insulin to be approved by the FDA. It was introduced in 2006 and withdrawn in 2007 because of poor sales. Novo Nordisk and Eli Lilly terminated their own inhaled insulin programs in 2008 and 2009, respectively. MannKind is currently preparing to resubmit its new drug application to the FDA after a request for additional information earlier this year. Only time will tell if inhaled insulin makes a comeback.

References

1. <http://www.mannkindcorp.com/afresa-background.aspx> accessed June 2010.
2. Daily highlights from the American Diabetes Association 70th Scientific Sessions. From June 25-29, the editors of *Medical Economics* and Advanstar Communications bulletins

Objectives for this Knowledge-based Activity:

- Describe Afrezza® studied use and efficacy
- Review the impact the results of the ACCORD trial will have on the management of patients with diabetes
- Discuss optimal vitamin D levels and dosing

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Summary of the Action to Control Cardiovascular Risk in Diabetes– Lipid Study

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Patients with Type 2 diabetes have an increased risk of developing cardiovascular disease.¹ This risk is estimated to be 2 to 4 times higher in patients with type 2 diabetes than those without.⁴ Cardiovascular disease prevalence in this population is attributed to the multiple co-morbidities that are typically present, including hypertension and dyslipidemia.² Dyslipidemia in type 2 diabetes often displays a somewhat unique pattern on lipid panels, with the hallmark features being decreased high-density lipoprotein (HDL) and elevated triglycerides.⁴ Low-density lipoprotein (LDL) values typically do not differ significantly from those of patients without type 2 diabetes, however poor diets and sedentary lifestyles often result in patients with diabetes having elevated LDL as well.

In effort to prevent cardiovascular disease (CVD) events, LDL cholesterol is considered to be the primary target by the American Heart Association and the American Diabetes Association.³ HMG-CoA reductase inhibitors, or statins as they are commonly known, have been well established in clinical trials as efficacious in reducing LDL cholesterol and reducing the risk of major CVD events in patients with diabetes.³ Despite a clear reduction in risk with statin therapy, patients with type 2 diabetes are not devoid of CVD risk after lowering LDL cholesterol.¹ This is especially true if the patient has the aforementioned lipid profile that is typical of patients with diabetes. It is not clear, however, whether or not adjunctive lipid therapy directed towards low HDL or elevated triglycerides will further reduce the risk of CVD events.¹

The results of the Action to Control Cardiovascular Risk in Diabetes lipid study (ACCORD Lipid) were published by the New England Journal of Medicine in March of 2010. The objective of the ACCORD Lipid study was to investigate whether the addition of a fibrate to statin therapy would reduce the risk of cardiovascular disease when compared to patients on statin monotherapy.¹ In this study, 5518 patients were randomly assigned to receive either simvastatin plus fenofibrate, or simvastatin plus placebo. Patients included in the ACCORD Lipid study had type 2 diabetes with a hemoglobin A1c greater than or equal to 7.5%.¹ If patients had evidence of clinical CVD, patients aged 40 to 79 were included, however, if subclinical CVD was present or at least two additional cardiovascular risk factors, the range was reduced to ages 55 through 79 years.¹ Patients were also required to have the following: LDL between 60 and 180 mg/dL; HDL less than 55 mg/dL for women and African Americans, or below 50 mg/dL for all other groups; and a triglyceride level less than 750 mg/dL if they were not receiving any lipid therapy, or less than 400 mg/dL if the patient was receiving lipid therapy.¹

The differences in baseline characteristics between the two treatment groups were not statistically significant.¹ Open-label simvastatin was initiated in all patients at the initial visit, while blinded, adjuvant therapy of placebo or fenofibrate 160 mg per day was started one month later.¹ Lipid panels were measured at 4, 8 and 12 months, then annually after the first year, and at the conclusion of the study.¹

The primary outcome was first occurrence of a major cardiovascular event, which was defined as nonfatal myocardial infarction, nonfatal stroke, or death from a cardiovascular event.¹ Secondary outcomes included a combination of primary outcomes plus revascularization or hospitalization for congestive heart failure; a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina; nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.¹ *The results of the ACCORD Lipid study did not demonstrate a significant reduction in CVD risk when simvastatin plus fenofibrate combination therapy was compared to simvastatin monotherapy.¹ No significant differences were found in the comparison of the safety profiles between the two treatment arms (Table 1).¹*

Table 1: Serious Adverse Effects

Serious Adverse Events (SAE)	Fenofibrate group (%)	Placebo group (%)	P-Value
Aches/pains, regardless of CPK	1110 (40.1%)	1115 (40.5%)	0.81
Aches/pains, CPK > 5x ULN	7 (0.3%)	8 (0.3%)	0.79
Aches/pains, CPK > 10x ULN	1 (0.04%)	2 (0.07%)	0.56
Any nonhypoglycemic SAE	54 (2.0%)	43 (1.6%)	0.27
Any myopathy /myositis /rhabdomyolysis SAE	4 (0.1%)	4 (0.1%)	1.00
Any hepatitis SAE	2 (0.1%)	0 (0.0%)	0.18
Any SAE attributed to lipid medications	27 (1.0%)	19 (0.7%)	0.24

As expected, the fenofibrate group demonstrated greater reductions in total cholesterol and triglycerides, and a greater increase in HDL (Table 2).¹ All findings in the chart below were statistically significant, excluding LDL, but these values do not point to any clinical significance.

Table 2: Lipid Values

Measured Criteria	Fenofibrate Group		Placebo Group		P-Value
	Baseline (mean in mg/dL)	Exit Visit (mean in mg/dL)	Baseline (mean in mg/dL)	Exit Visit (mean in mg/dL)	
LDL	100.0	81.1	101.1	80.0	0.16
HDL	38.0	41.2	38.2	40.5	0.01
Triglycerides	189.0	147.0	186.2	170	<0.0001
Tot. Chol.	174.7	151.1	175.7	153.7	0.02

The primary outcome measure, which was first occurrence of a major cardiovascular event, occurred less frequently in the combination therapy group than the statin monotherapy group (Table 3).¹ However, neither the difference in the rate of primary outcomes, nor the differences in rate of secondary outcomes were statistically significant.¹

Table 3: Primary and Secondary Outcomes

Outcome	Fenofibrate (no. of events)	Placebo (no. of events)	Hazard Ratio (95% CI)	P-Value
Primary Outcome	291	310	0.92 (0.79-1.08)	0.32
Secondary Outcomes				
Primary outcome plus revascularization or hospitalization for CHF	641	667	0.94 (0.85-1.05)	0.30
Major coronary disease event	332	353	0.92 (0.79-1.07)	0.26
Nonfatal myocardial infarction	173	186	0.91 (0.74-1.12)	0.39
Stroke				
Any	51	48	1.05 (0.71-1.56)	0.80
Nonfatal	47	40	1.17 (0.76-1.78)	0.48
Death				
Any cause	203	221	0.91 (0.75-1.10)	0.33
Cardiovascular cause	99	114	0.86 (0.66-1.12)	0.26
Fatal or nonfatal CHF	120	143	0.82 (0.65-1.05)	0.10

The results of the ACCORD Lipid study disproved the hypothesis that the addition of fenofibrate to statin therapy provided additional cardiovascular benefit in patients with type 2 diabetes despite increasing HDL and decreasing triglycerides.¹ Although the fenofibrate plus simvastatin combination therapy did significantly improve lipid profiles when compared to simvastatin monotherapy, these values are not compelling enough to warrant a change in practice. This is reinforced by the fact that the reductions in primary and secondary outcomes that occurred in the combination therapy group were not significant.

Although the results of the ACCORD Lipid study do not support the ubiquitous use of fibrate-statin combination therapy in patients with type 2 diabetes, this does not mean that such a combination is never indicated or should not be further studied. The ACCORD Lipid study encompassed patients with a very wide range of lipid profiles, so one cannot rule out the possibility of a mortality benefit in a smaller subgroup of patients with a narrower range of particular lipid values.

Patients with type 2 diabetes often must endure a barrage of medications upon diagnosis. This regimen typically includes glycemic agents, aspirin therapy, antihypertensives, renally-protective agents, and lipid-lowering agents, in addition to any medications that may be present to treat other disease states. *The ACCORD Lipid study is important to clinical practice because it demonstrated that statin monotherapy is sufficient treatment for dyslipidemia in the general population of patients with type 2 diabetes, and can prevent the addition of medications without a proven mortality benefit.*

References

1. Accord Writing Committee: Ginsberg HN, Elam MB, et al. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *New England Journal of Medicine* 2010; 10.1056/NEJMoa1001282.
2. Brunzell JD, Davidson M, et al. Lipoprotein Management in Patients With Cardiometabolic Risk. *Diabetes Care* 2008; 31: 811-822.
3. Buse JB, Ginsberg HN, et al. Primary Prevention of Cardiovascular Diseases in People With Diabetes Mellitus. *Diabetes Care* 2007; 30: 162-172.
4. Haffner SM. Management of Dyslipidemia in Adults With Diabetes. *Diabetes Care* 2003; 26: S83-S86.

Answers to the most common Vitamin D Questions

What is all the discussion regarding Vitamin D about?

Vitamin D is important for more than just bone health. Recent studies have strengthened the evidence that adequate vitamin D intake may help prevent cardiovascular disease, cancer, and diabetes.¹ It may improve muscle strength and prevent falls.² In the June 20th issue of Endocrine Today, a study of 1,289 elderly men and women has found a link between vitamin D deficiency and elevated risk for metabolic syndrome. The study demonstrated that older people with a serum 25-hydroxyvitamin D (25-OH D) level below 50 ng/mL had a higher risk for metabolic syndrome compared to people with a level higher than 50 ng/mL. The association was primarily determined by the risk factors of low HDL and increased waist circumference. Based on their findings, the researchers suggested that adequate levels of vitamin D may help prevent metabolic syndrome.³ As research increases our understanding of the relationship between vitamin D and health, questions are arising about adequate vitamin D intake. Particularly in our geographic location considering most patients receive Vitamin D from sun exposure.

What is the best measure of vitamin D?

The best measure of vitamin D is 25-(OH) D levels. Calcium, parathyroid hormone, or other tests are not always accurate to detect a deficiency.

What is an optimal vitamin D level?

Optimal blood levels of 25-(OH) D for bone health are at least 30 ng/mL, normal levels can reach 100 ng/mL. Vitamin D levels below 20 ng/mL are considered deficient. Vitamin D toxicity is very rare and usually not a problem until levels exceed 150 ng/mL.

What therapy is recommended if a patient's vitamin D level is suboptimal?

For vitamin D deficient patients, 50,000 units (IU) of vitamin D2 (ergocalciferol) can be given once weekly for 6-12 weeks for replenishment.⁴ This regimen can be repeated if levels do not reach 30 ng/mL. For maintenance, vitamin D2 1000-2000 IU can be given daily or 14,000 IU once a WEEK or 50,000 IU once a MONTH. Now that so many more people are taking vitamin D, some are asking how much vitamin D is too much. Toxicity can occur with excessive doses such as 50,000 IU/day for several months for adults.

Who should have a Vitamin D level checked?

Consider testing for patients who are likely to be deficient such as elderly housebound individuals, those with renal disease or persistent nonspecific musculoskeletal pain.

Why are so many people deficient in vitamin D?

Sunscreens, staying in doors, living in northern latitudes have decreased exposure to the sun. It is difficult to get adequate vitamin D from foods. Even milk fortified with vitamin D contains only about 100 I per cup.

What are the various forms of vitamin D?

Many vitamin D supplements contain vitamin D2 (ergocalciferol), but vitamin D3 (cholecalciferol) is better at raising and maintaining vitamin D levels. Fracture prevention studies used vitamin D3. The Osteoporosis Society of Canada recommends D3. Patients with advanced renal disease have impaired conversion of vitamin D3 to its active form, calcitriol. These patients typically require supplementation with calcitriol 0.25 mcg daily or more.¹ However, you still may see more patients on D2 (ergocalciferol) due to insurance coverage.

References:

1. Vitamin D and calcium: not just for bones anymore. Pharmacist's Letter/Prescriber's Letter 2007;23(7):230708.
2. Wolpowitz D, Gilchrist BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol 2006;54:301-17.
3. The Endocrine Society 92nd Annual Meeting. Endocrine Today, Low vitamin D may be risk factor for metabolic syndrome, accessed June 24, 2010 <http://www.endocrinetoday.com/view.aspx?rid=65688>
4. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.

Goal

- The goal of the Diabetes Dispatch is to increase the reader's knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.

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ALASKA NATIVE DIABETES PROGRAM



Continuing Education Quiz

Diabetes Dispatch: Summer 2010

- 1) Afrezza® is typically used with what other insulin formulation?
 - a. Insulin aspart
 - b. Insulin glargine
 - c. Insulin detemir
 - d. Insulin lispro
- 2) Afrezza® offers what benefits thus far in clinical trials vs. twice-a-day premixed insulin?
 - a. Less hypoglycemic episodes
 - b. Less weight gain
 - c. Fewer injections
 - d. All of the above
- 3) A unique lipid presentation commonly seen in type 2 diabetes includes:
 - a. A decreased LDL level and an elevated HDL level
 - b. Elevated triglycerides and a decreased HDL level
 - c. Elevated HDL and elevated triglycerides
 - d. Elevated total cholesterol and an elevated HDL
- 4) The risk of developing cardiovascular disease in a patient living with type 2 diabetes is ___ to ___ times that of a person living without.
 - a. 3 to 6
 - b. 1 to 3
 - c. 2 to 4
 - d. Exactly the same
- 5) Which lipid parameter is deemed by the American Heart Association and the American Diabetes Association as the one that is the primary target in order to prevent CVD events?
 - a. LDL
 - b. VLDL
 - c. HDL
 - d. Triglycerides
- 6) Vitamin D has more indications than just bone health. What are some other disease states that are positively impacted by this vitamin as noted by recent literature?
 - a. Diabetes
 - b. Cancer
 - c. Cardiovascular disease
 - d. All of the above
- 7) The best measure of vitamin D is 25-(OH) D levels. What is the optimal level of this measure in the blood?
 - a. 30-100 ng/dL
 - b. 10-100 ng/dL
 - c. 100-150 ng/dL
 - d. > 150 ng/dL
- 8) True or False– Vitamin D2 (ergocalciferol) is more efficient than vitamin D3 (cholecalciferol) in raising and maintaining vitamin D levels.
- 9) At what blood level is vitamin D considered toxic?
 - a. 30-100 ng/dL
 - b. 10-100 ng/dL
 - c. 100-150 ng/dL
 - d. > 150 ng/dL

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LESSON EVALUATION

	Disagree	Agree		Disagree	Agree
1) Activity met learning objectives	1	2 3 4 5	4) Activity learning assessment appropriate	1	2 3 4 5
2) Amount of time was appropriate	1	2 3 4 5	5) Author was knowledgeable in topic	1	2 3 4 5
3) Increased my knowledge of topic	1	2 3 4 5	6) Overall, I was satisfied with the activity	1	2 3 4 5

To obtain CPE credit for this lesson you must answer the questions on the quiz (70% correct required). Should you score less than 70%, you will be asked to repeat the quiz. In May and November of each year we will mail a statement of credit, unless otherwise arranged with the AkPhA office.

This knowledge-based activity is accredited for 1.0 hours of continuing pharmacy education (0.1 CEU). Pharmacists and technicians may receive credit for completing this lesson if returned by 7/20/2013. ACPE #0139-9999-10-018-H01-P AkPhA#0139-9999-10-018-H01-T

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