



## DIABETIC INVESTOR



**“Make the Connection”**  
**David Kliff, Publisher**

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Will 2004 finally be the year Exubera is submitted to the FDA for approval? Does Exenatide have a chance at becoming the next blockbuster drug used to treat Type 2 patients? Will Bristol-Myers Squibb transform itself into a major player in the diabetes market? Can anyone stop the runaway success of Lantus? These are just some of the questions Diabetic Investor will attempt to answer as we look ahead to the New Year.

It seems odd, in a way, that as we complete 2003 and look ahead towards 2004, everyone is still talking about inhaled insulin. After all, this is a product which was supposed to be on the market already; a product which was supposed to rack up billions in sales; a product that would change diabetes treatment forever by taking away the painful regimen of daily insulin injections. Yet, here we are left wondering if inhaled insulin isn't the technology equivalent to a non-invasive glucose monitoring system; something everyone seems to be working on but no one seems to be able to get to actually work in the real world.

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The leading candidate in the field continues to be Exbuera, a collaboration between Pfizer (NYSE:PFE) and Aventis (NYSE:AVE). Pfizer is also collaborating with Nektar Therapeutics (NASDAQ:NKTR). When Diabetic Investor last commented on Exubera, we basically said there was little chance that the FDA would approve the product, and we wouldn't be surprised if the project was terminated outright. As regular readers know, Exubera has had something of a troubled history. But this hasn't stopped many in the analyst community from continuing to believe that Exubera will be a blockbuster product. Some have even gone so far as to comment that Exubera will soon be submitted to the FDA and may already be submitted for approval in Europe.

While neither Pfizer or Aventis will publicly comment on when or if Exubera will be submitted for FDA or European approval, both companies continue to publicly back the product.

Yes, a non-injectable form of insulin would benefit millions of patients who are unable to control their diabetes using diet or oral medications. And yes, the fact that all the current versions of insulin must be injected is a barrier to insulin therapy. The fact of the matter is that even if by some miracle Exubera is approved, this is not a blockbuster drug. In simple terms, Exubera is already dead on arrival. Why? With Exubera's checkered history, it's unlikely physicians will be willing

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**Exubera-  
Besides safety concerns  
the delivery device could  
turn off patients.**

to prescribe the drug. Many of these same physicians were burned once before when they prescribed Rezulin, once considered a best in class oral medication for Type 2 patients. Not unlike Exubera, there were also questions regarding Rezulin's safety, even though the drug received FDA approval. As it turned out, these safety concerns were legitimate and Rezulin eventually was pulled from the market. (In a strange twist of fate, Pfizer is now the subject of several class action lawsuits involving Rezulin. Pfizer picked up this liability when they bought Warner-Lambert, Rezulin's original owner.)

Even without the many safety issues surrounding Exubera, there's still the problem with the drug's delivery device. Keep in mind that Exubera is an inhaled version of short-acting insulin. This type of insulin is taken at mealtime or before a heavy snack. For most patients, that means Exubera would be taken at least three times each day. Insulin injections may not be pleasant (speaking from experience, Diabetic Investor would even go so far as to say they're really not that painful), but injections are relatively easy to administer. One only has to take a look at Exubera's delivery device (pictured on this page) to see that it's not something that would be easy to carry around all day. It should come as no surprise that during the many clinical trials involving Exubera, there was higher than normal dropout rate and the number one reason given by subjects was the difficulty in using the delivery device.

Finally, Exubera is likely to face stiff competition from a new drug likely to be on the market that is also targeted at Type 2 patients. And, unlike Exubera, this drug will come to mar-



Photo Courtesy of Nektar Therapeutics

ket with few, if any, safety issues and although injectable, will be simple to take. Look for Exenatide (from Amylin Pharmaceuticals (NASDAQ:AMLN) and Eli Lilly (NYSE:LLY)) to go before the FDA in mid-2004. Diabetic Investor sees Exenatide receiving FDA approval and becoming marketable in early 2005.

*Driving Exenatide's future success are three key factors:*

**1. Patients on Exenatide showed significant improvement in lowering their A1C levels.**

**2. Patients also showed statistically significant reductions in body weight.**

**3. Patients on Exenatide inject the same amount of the drug twice a**

**day regardless of their current glucose levels or expected meal intake.**

While the first two points are reason enough to believe in Exenatide's future success, the ease of delivery will go a long way towards overcoming physicians' and patients' reluctance to inject. Both Amylin and Lilly are well aware of this fact, which is why Exenatide's delivery system will be a pen. The Exenatide pen will be even easier to use than the many insulin pens already available. The patient will simply select one or two dosage levels and shoot. (During the trials, patients started with dosage levels of 5 micrograms, which after a month were increased to 10 micrograms. According to Amylin, this regimen is designed to lessen the mild nausea, which was the most commonly reported adverse event.)

The importance of a simple to use delivery device cannot be underestimated. Unfortunately, nearly 80% of diabetes patients in America are treated by their primary care physician, not a diabetes specialist who is more likely to prescribe insulin. Primary care physicians are often reluctant to prescribe insulin due to the fact that not only is insulin injected, but also because patients on insulin therapy require additional training. This is something that takes time, and the majority of primary care providers lack the time and staff to properly train patients on administering insulin. This problem will be greatly reduced by Exenatide's easy to use delivery system and level dosage regimen. Unlike insulin users, patients on Exenatide don't need to worry about what their glucose levels are or what they plan on eating before they inject. They'll take the same amount regardless.

While some patient education will be

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Make the Connection from page 2 needed, it's nowhere near the level of what a first time insulin user needs.

Also helping overcome physicians' resistance to prescribing any injectable drug is the weight loss factor. An unfortunate side effect of insulin therapy is weight gain. Patients taking insulin typically experience weight gain as their body begins to process sugars more efficiently. In effect, the greater they control their diabetes, the more likely it is they'll experience weight gain. This is not the case for patients taking Exenatide, who during trials showed weight loss. This one fact alone could be the over-riding factor in overcoming resistance to injections. As everyone knows, Americans in particular are obsessed with their weight and will do almost anything to lose weight.

But Exenatide is only the appetizer in Amylin's pipeline; the real meal is the long acting version Exenatide LAR. The company is currently working on a version of Exenatide that would require as few as two or possibly one injection per month. Talk about overcoming the hurdle of being an injectable. Patients may be reluctant to inject twice a day to achieve greater control, but that level of resistance should drop dramatically when only one or two injections are needed each month.

Suffice it to say, Diabetic Investor sees a bright future for Amylin and their shareholders.

From a diabetes perspective, the same can be said for Aventis, the makers of Lantus. Since its introduction in 2001, Lantus has become the leading insulin brand in the United States, claiming 19.6% of total pre-

scriptions in the U.S. insulin market. Not only has Lantus enjoyed tremendous commercial success, it's had a dramatic affect on several of Aventis' competitors. During their third quarter conference call, Lilly acknowledged that Lantus' success was cutting into sales of their leading insulin, Humalog. Medtronic (NYSE:MDT), the owners of insulin pump maker MiniMed, has also acknowledged that Lantus is harming

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its efforts to grow their insulin pump business. Novo Nordisk (NYSE:NVO) is seeking approval for their long acting insulin, Detemir, but most experts agreed that Detemir will do little to stop the Lantus juggernaut.

Looking to expand their dominance in the long acting arena, look for Lantus to soon be available with a pen delivery system here in the United States. Already available in Europe, a pen delivery system will only enhance Lantus' sales.

Not content to sit on the success of Lantus, Aventis has also submitted short acting insulin, Apidra, for FDA approval. With the expected approval of Apidra, Aventis will be in the position to compete head on with Lilly and Novo-Nordisk in the insulin market; a market that is likely to grow

more rapidly based on a number of positive trends:

**1. While some might not consider the epidemic growth rate of diabetes a positive trend, this is a fact.**

**2. Insulin therapy is gaining wider acceptance and not just in the Type 1 patient population. Based on data released this past April, 77% of the patients using Lantus fall into the**

**Type 2 category. This is up from 66% from the December 2002 data.**

**3. Insulin is becoming a front line therapy, no longer used as the treatment of last resort.**

**4. While estimates vary, Diabetic Investor sees the number of insulin users in America to be between 3 to 4 million patients, with 150,000 or so added each year. Worldwide, it's estimated that nearly 20 million patients are using insulin, making insulin a global market worth nearly \$5 billion.**

These trends are also the reasons that all the major insulin players are publicly committed to developing alternate delivery options for insulin. As previously mentioned, Aventis is partnered with Pfizer on Exubera.

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Novo Nordisk is working with Aradigm (NASDAQ:ARDM) on their version of inhaled insulin and Lilly is partnered with Alkermes (NASDAQ:ALKS). As noble as these efforts may be, Diabetic Investor does not see any of these projects having a substantial impact on the market for some time, if ever. The winners and losers in the insulin market are more likely to be determined by the size of the company's sales forces and the strength of their pipelines.

In terms of insulin, the real loser appears to be Lilly. With no long acting insulin anywhere near approval and increasing competition from both Novo and Aventis in the short acting area, Lilly's once dominant position will continue to erode. From outward appearances, Lilly wants to use their partnership with Amylin on Exenatide to form the basis for a new direction in their diabetes business. In some respects, Exenatide could change the market just as Lantus has done. This will be particularly true should the long acting version of Exenatide work as well as the current version.

Under this scenario physicians would be faced with the choice of putting their Type 2 patients on once a day Lantus, which can be used in combination with oral medications, or the once or twice a month version of Exenatide. At first glance, the long acting version of Exenatide would appear to have the advantage based on the lower frequency of injections. Conversely, Lantus has already established itself, and getting patients to switch from an existing proven treatment option isn't easy. This, of course, is all mere speculation, as Exenatide in any form has not reached the FDA.

It's not speculation to say that

The Lantus Pen- Currently available in Europe with an updated version coming to America. This easy to use delivery system will only enhance Lantus sales.



Aventis and Novo are clearly setting their sights on each other. Detemir may not be the insulin that Lantus is, but Novo's delivery systems are the best in the business. Once an also-ran here in the United States, Novo has made significant inroads here. Their partnership with Wal Mart (Novo provides the Reli On brand of insulin) has paid big dividends, and they also have a partnership with Johnson and Johnson's Lifescan division.

In fact, it would not surprise Diabetic Investor if the consolidation in the diabetes sectors continues with J&J one day buying Novo and Lilly buying Amylin.

Nor will Aventis sit still as they could easily add to their diabetes pipeline with their own deals. It's no secret that Aventis is interested in an oral form of insulin and could well announce a venture with Emisphere Technologies (NASDAQ:EMIS) along these lines. (It should be noted that Diabetic Investor sees an oral form of insulin as a long shot possibility at best.) No matter, the one fact that's as clear as crystal is Aventis has firmly established itself as a formidable player in the diabetes sector.

Another company looking to establish, or should we say re-establish, itself as a player in the diabetes sector is Bristol-Myers Squibb (NYSE:BMJ). Once the leader in Type 2 oral medications with Glucophage, the company has had a difficult time since the drug went

Photo Courtesy of Aventis generic. Looking to change all that, the company has made several deals in the sector. In the span of just a few weeks, the company announced two deals in the diabetes space. First came an agreement with Flamel Technologies (NASDAQ:FLML) for their long acting insulin, Basulin. Second, and also in the insulin area, came an agreement with Qdose, a joint venture between MicroDose Technologies, Inc. and Quadrant Drug Delivery, Ltd., to develop an inhaled form of insulin. Diabetic Investor has also learned that the company is near a deal with Metrika, the makers of the A1Cnow disposable A1C test. Finally, Bristol took a look at meter maker Therasense (NASDAQ:THER) but decided against buying the company.

With the exception of the upcoming deal with Metrika, Diabetic Investor sees Bristol's efforts as being off the mark. Even if Basulin worked as well as Lantus, it would still be third to market behind Novo's Detemir should it make it to market.

The deal for inhaled insulin is even more perplexing. Not only are they well behind the many players in this area, but there are as many candidates in the race to develop inhaled insulin as there are seeking the Democratic Presidential nomination; there remains serious questions if any inhaled insulin will ever make it to market.

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At this stage, it appears to Diabetic Investor that the company's efforts to re-establish their place among the players in the diabetes sector is still a long way off.

### **Are injections really that much of a barrier to a product's ability to achieve commercial success?**

Inhaled, oral, liquid and transdermal patch - these are just some of the alternate delivery systems being worked on for insulin. The theory behind all of these alternate delivery systems is that insulin therapy would be an easier sell if it didn't have to be injected. On the surface, it's hard to argue with the theory. After all, if someone asked the nearly 20 million patients on insulin therapy if they would prefer a non-injectable form of insulin, the answer would be a resounding yes.

Think for a moment what a patient on insulin goes through on a daily basis. Typically, insulin is taken prior to each meal and, for many patients, there's the additional injection of Lantus once each day - that's four injections each and every day, 365 days a year. That's 1460 injections each and every year. And that doesn't count the off meal injections many insulin users take before snacks.

Over the past few years, research has shown that patients on multiple daily injection (MDI) therapy achieve greater control and therefore delay, or even prevent, the many complications associated with diabetes. Some patients on MDI can take as many as six or seven or more insulin injections each day.

But that's only half the story. The

amount of insulin injected can vary based on several factors such as current glucose levels, expected meal intake, etc. So, not only does the patient inject insulin four or more times each day, there's also the added burden of testing glucose levels before each insulin injection. This is the main reason insulin users are coveted by the makers of glucose monitors as they are the most frequent testers. There's a reason why, when I explain to people what it's like to have diabetes, I tell them it's like being a human pin cushion. With the amount of times we stick our bodies, either to take insulin or test our blood sugars, it's a miracle we don't leak when we drink something.

There's no question that an alternative to injections would be preferable. But this fact really has nothing to do with the so-called pain of injecting, the most frequent argument used by the many companies looking to develop alternate delivery systems. In reality, it's more painful for someone with diabetes to treat their glucose levels than it is to inject insulin. There are several reasons for this, but two stand above the rest. First, advances in needle technology. For example, the needles I use for my insulin pen and syringes are both lubricated. Today's needles are also shorter and thinner. Second, insulin is not injected into areas where there is a lot of muscle tissue. Typical insulin shooting zones are the abdomen, upper legs and rear - all areas where there is a heavy concentration of fatty tissue. This is not to say injections are pain-free, but, in reality, injections really can't be considered painful.

The real reason many physicians are reluctant to prescribe insulin has more to do with the fact that patients

must be educated. As pointed out earlier, patients don't simply dial out a dose on their insulin pen or syringe. Dosage levels can vary, which means patients must understand when to increase or decrease the amount they take. This requires patient education. Insulin users need to understand how their bodies work so they do not administer too much or too little insulin. Regardless of how insulin is administered, injections, inhaled, patch or pill, patients will still require education - insulin is not a one-dose-fits-all therapy.

Diabetic Investor believes the success of Lantus, in particular with Type 2 patients, goes a long way towards dispelling the notion that just because a drug is injected, it cannot achieve commercial success. For similar reasons, we believe Exenatide will be another drug that reaches commercial success, even though it, too, is an injectable. The bottom line here is patients and their physicians want drugs that help control their diabetes and, while they may prefer an alternative to injections, this one fact alone won't stand in the way of success.

Diabetic Investor, Inc.  
603 Hackberry Ct East  
Buffalo Grove, IL 60089

[dkliff@diabeticinvestor.com](mailto:dkliff@diabeticinvestor.com)  
[www.diabeticinvestor.com](http://www.diabeticinvestor.com)

800-783-3712  
847-634-4777  
847-634-4646 Fax  
224-715-3761 Mobile

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