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DIABETIC INVESTOR



“Make the Connection” David Kliff, Publisher

April 2006

“Our forecast of global Exubera sales of \$1.7b in 2008 and \$2.0b in 2010 are at the high end of Street consensus, but our 2H 2006 sales forecast of \$186m is significantly lower than the consensus of \$257m, which appears overly aggressive considering the likely strong push-back from third-party payers following launch.” -

Datamonitor March 31, 2006

“We raised our 2007-2010 worldwide estimates for Exubera to \$493 million, \$854 million, \$1,257 million and \$1,560 million based on the results of our survey and our new patient model (up from \$350 million, \$600 million, \$800 million and \$940 million).”-

Goldman Sachs April 11, 2006

“What we anticipate seldom occurs, what we least expected generally happens.” -

Benjamin Disraeli (1804-1881)
English Statesperson and novelist.

Based on the statements made by Datamonitor and Goldman Sachs, it appears Diabetic Investor once again stands alone in our prediction that Exubera, the inhaled insulin from Pfizer (NYSE:PFE) and Nektar Therapeutics (NASDAQ:NKTR), will fail to reach blockbuster status. Diabetic Investor does see a place for Exubera; however, we view the predictions that Exubera sales will reach \$2 billion by 2010 as overly optimistic.

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Since receiving approval back in January, the Street has been trying to determine Exubera’s sales potential. The basis for the current estimates appears to come from physician interviews. Both *Datamonitor* and *Goldman Sachs* anticipate that physicians will embrace Exubera, in particular, for their type 2 patients.

Goldman Sachs states, “Our view is that early adopters will drive use in adult Type II diabetics to 15% by 2010”. *Datamonitor* projects that by 2010, 20% of diagnosed type 1 patients will be using inhaled insulin, 25% of type 2 insulin starters will use inhaled insulin, and 5% of type 2 failing oral therapies will use inhaled insulin. In total, *Datamonitor* projects that by 2010 there will be 1.47 million patients using inhaled insulin and Exubera will garner 49% of these patients.

Neither *Goldman Sachs* nor *Datamonitor* believes that Exubera will achieve these projections without overcoming some hurdles. According to *Datamonitor*; “With the cost expected three or four times higher than injected insulin, Exubera’s reimbursement is likely

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to be very poor (Tier 3 level) or non-existent among managed care plans.” *Goldman* points out that physicians are concerned over the long-term effects about lung function, although they don’t see this as a serious obstacle.

Underlying both reports is the fact that Exubera is a non-injectable form of insulin. Diabetic Investor is not aware of any physician or researcher who is not cognizant of the beneficial effects of insulin therapy. Until the approval of Exubera, there were only two ways to administer insulin, injections or insulin pump. As *Goldman* points out, “The central patient need is still intact: Patients do not like needles.” They go on to state, “We continue to believe that this is a key variable that will drive important use of the product.”

This is the key to the entire analysis of Exubera and the driving force behind these optimistic sales forecasts. Take away the fact that Exubera is non-injectable and you would have just short-acting insulin. In fact, you would have a short-acting insulin that really doesn’t work that well. According to a study published in the June 2004 issue of *Diabetes Care* entitled “Patient Satisfaction and Glycemic Control After 1 Year With Inhaled Insulin (Exubera) in Patients With Type 1 or Type 2 Diabetes”, “At the end of the 12-week parent studies, the mean adjusted differences between changes in HbA1c were similar for both treatment regimens in patients with type 1 diabetes (inhaled -0.69%; subcutaneous -0.85%) and type 2 diabetes (inhaled -0.61%; subcutaneous -0.79%).” Baseline HbA1c levels for this study were 8.5% for both groups.

Also published in the November 2004 issue of *Diabetes Care* was a study entitled “Efficacy and Safety of Inhaled Insulin (Exubera) Compared with Subcutaneous Insulin Therapy

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in Patients with Type 1 Diabetes.” According to this study, “Baseline HbA1c values were 8.1% in both groups. At week 24 (last observation carried forward), HbA1c was 7.9% in the inhaled insulin group and 7.7% in the subcutaneous group”

In the October 2004 issue of *Diabetes Care* was published the study entitled “Efficacy and Safety of Inhaled Insulin (Exubera) Compared with Subcutaneous Insulin Therapy in Patients with Type 2 Diabetes.” According to this study, “Mean HbA1c decreased similarly in the two treatment groups. After 24 weeks of treatment, mean HbA1c levels decreased from 8.1% at baseline to 7.4% at week 24 in patients receiving inhaled insulin. Patients receiving subcutaneous showed a decrease from 8.2% to 7.6%.”

As these three studies accurately point out, Exubera does not work any better than subcutaneous delivery of insulin. As a point of fact, Pfizer has never claimed that Exubera worked any better than conventional insulin injections. The company has consis-

tently stated that Exubera worked as well as injected insulin. When one considers the fact that the American Diabetes Association (ADA) defines a diabetes patient as being under good control when their HbA1c level is 7% or below, neither Exubera nor injected insulin therapy was very successful.

Diabetic Investor sees several reasons that both Exubera and injected insulin failed to produce better patient outcomes.

1. In two of the studies, the patients on injection therapy were administered a bedtime dose of Ultralente or at least two daily injections of regular and NPH insulin. (The authors of the June 2004 study did not disclose which insulin they used for those patients taking injections.) Diabetic Investor believes that those patients in the injection groups would have achieved better outcomes had they been administered the long acting insulin Lantus and either NovoLog or HumaLog for their short-acting insulin. All three are insulin analogs which now account for over half the insulin market share. These newer insulins have proven extremely effective and are the primary reason why older insulins such as Ultralente and NPH continue to see their share numbers decline. Simply put, insulin analogs work better.

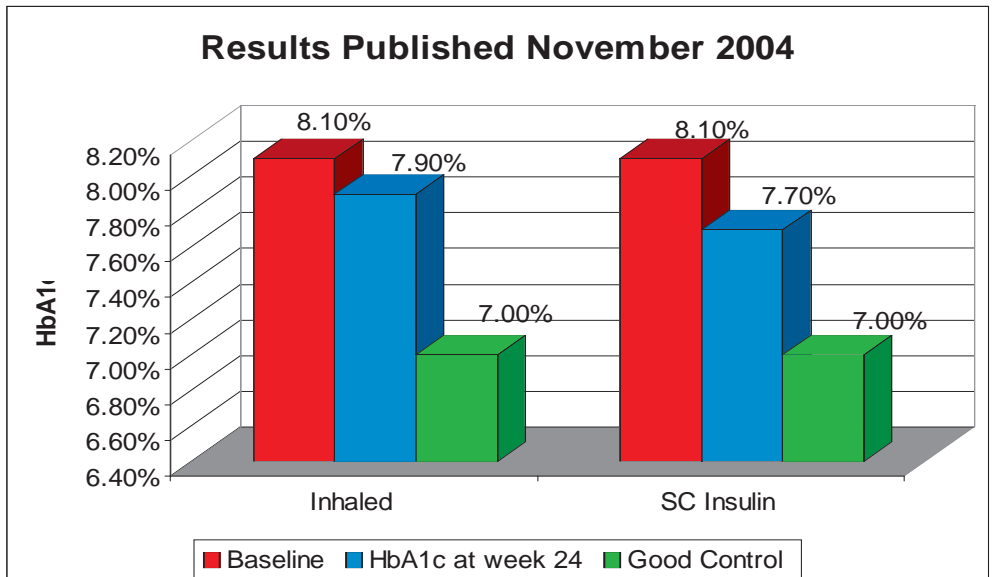
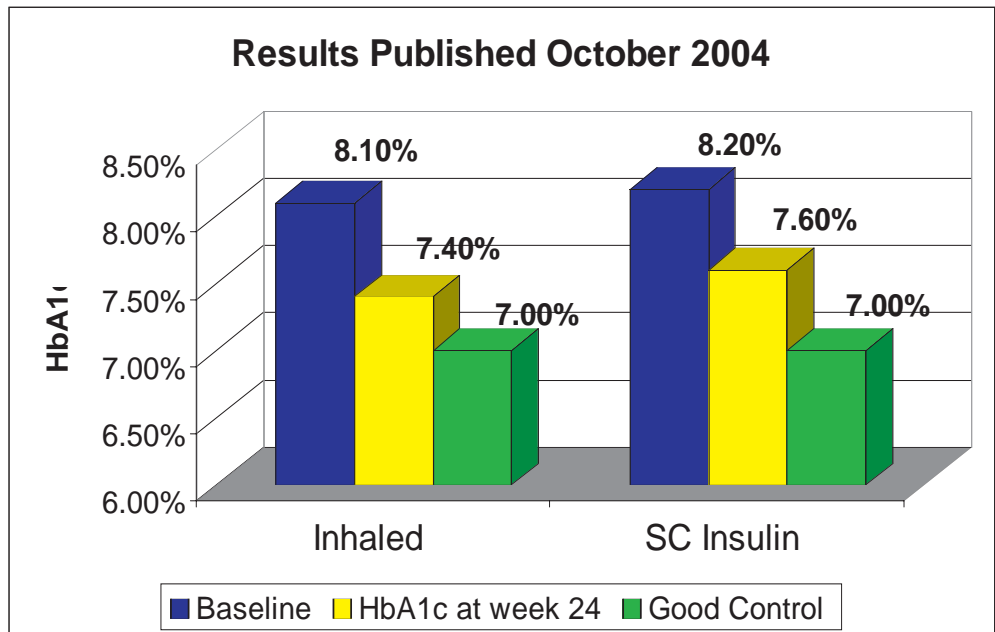
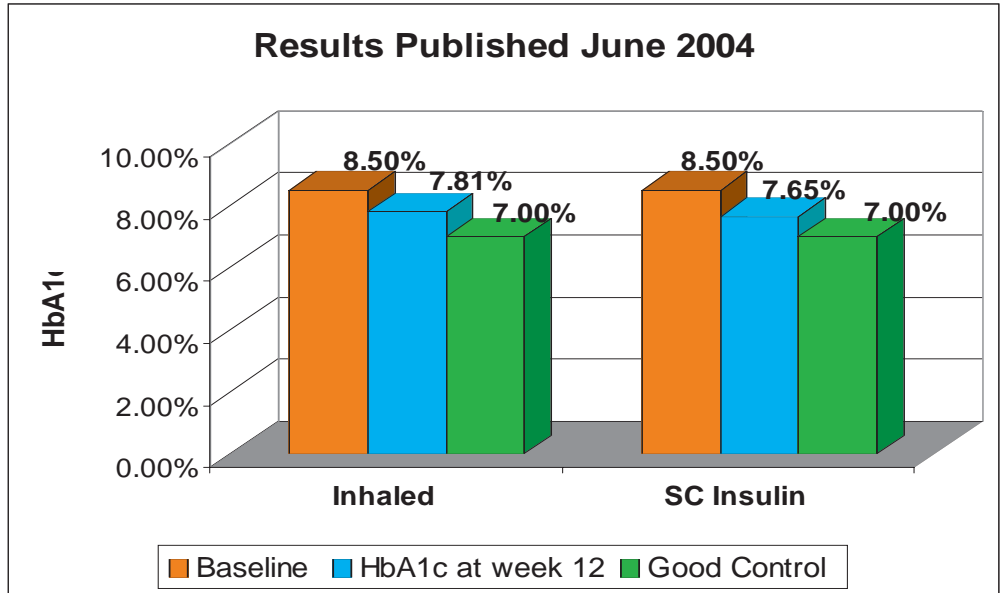
2. Reaching an HbA1c level of 7% or below is more than just which treatment regimen is chosen. Diet and exercise also play a key role.

3. Insulin, regardless of how it is administered, in and of itself, does not guarantee that patients will achieve good control. The key is

It's interesting to note that Pfizer never claimed that Exubera worked better than injected insulin, merely that it produced outcomes similar to injected insulin. As the charts on this page indicate in three different studies, all published in *Diabetes Care*, patients using Exubera did achieve outcomes similar to those taking insulin injections. Yet, for all the hype surrounding Exubera, the elephant in the room that no one seems to notice or wants to talk about, is that neither the patients on Exubera nor those taking injected insulin achieved good control as defined by the American Diabetes Association (ADA). Since when is a drug that fails to produce better outcomes considered a candidate to achieve blockbuster status?

administering the proper amount of insulin at the proper time. Unlike oral medications which are taken in fixed doses, the variability of insulin dosing is critical. The fact that in all three studies the results were sub-standard proves just how difficult it is to reach good control. Insulin therapy requires that patients be educated on how food intake, exercise and outside factors such as stress affect insulin intake. It's also important to note that these factors need to be combined with the patients glucose levels when determining how much insulin should be administered.

4. Frequency of insulin delivery is another critical factor. Taking insulin at meal time alone may not be adequate to achieve control. It is not uncommon for patients on multiple daily injection (MDI) therapy to inject four or more times each day. The fact is insulin should be administered not just with meals but with snacks or when glucose levels fall outside of a predetermined range.



5. Fear of hypoglycemia, low blood sugar, is another contributing factor. Hypoglycemia can lead to serious consequences and possible death. Both the physician and the patient are aware of this and as a result the recommended dosing schedule is designed to avoid hypoglycemic events. Understanding that type 2 patients, in particular, are not diligent when it comes to testing their glucose levels, it is not unusual for a physician to recommend a fixed dosing schedule for their type 2 patients taking insulin.

It would be fair to say that if someone looked at the results of these studies and did not know that one group was taking Exubera and the other subcutaneous insulin, they would not be particularly impressed by the results. While there were reductions in HbA1c in both groups, the results can hardly be classified as being successful.

This brings us back to the underlying premise made by not only the Goldman and Datamonitor reports but the Street in general in that, the mere fact that Exubera is inhaled rather than injected is enough to make the product commercially successful. It stands to reason then to examine Exubera's delivery device as it plays a critical role. Keep in mind that Exubera is short-acting insulin, insulin which is supposed to be taken at mealtime and with snacks. Therefore, it would not be unusual for a patient to use the device at least three or more times each day. That's each and every day; there are no days off when a patient is on insulin therapy.

Given the fact that during clinical trials patients on Exubera failed to achieve better outcomes than those taking insulin injections, the optimism for its future commercial success lies in the perception that physicians and their patients are more likely to adopt insulin therapy because they would not experience the "pain" of injections. While it is true Exubera patients would not have to inject insulin, it's an open question if using Exubera is really any easier for the patient. The size and complexity of Exubera's delivery device, pictured below, could be its Achilles heel.



It also makes sense to compare the device to competing delivery systems. With the approval of Exubera, physicians and patients now have a fourth choice on how their insulin will be administered. Short-acting insulin can now be delivered using a syringe, insulin pen, insulin pump or inhaled. Being intimately familiar with all the delivery options with the exception of Exubera, Diabetic Investor has graded the various delivery systems in 7 different categories. The grades for the Exubera

Photo courtesy of Pfizer
delivery device are based on information available in the public domain. The categories are:

Reimbursement – Grades were determined based on the patients' likely out of pocket expense and ease of which the device is covered. This would explain why insulin pumps received a C+; although the reim-

bursement process for insulin pump therapy has improved over the years, several payers still require patients jump through some hoops before granting reimbursement. However, there is little or no additional paperwork required for patients who use a syringe or insulin pen. While reimbursement for Exubera has yet to be determined, the general consensus appears to be that it will not receive levels comparable to syringes or pens, therefore resulting in a higher out of pocket expense for the patient.

Ease of Use - Here we looked at how long, after determining the amount of insulin needed, did it take to administer the insulin; the steps that were required. Here the insulin pen is by far the easiest device to use. The patient simply dials out the dose and shoots. Next is the syringe, where the patient must fill the syringe from an insulin vial. The grade for insulin pumps is a bit misleading; once educated in pump therapy, using a pump is simple; however, there is a fair amount of education required to learn how to use a pump properly. The Exubera grade was determined after reading the label for the product; with so many steps involved, Diabetic Investor sees a high probability for user error.

Dosing Accuracy - As mentioned earlier, it's critical that the patient actually receive the proper amount of insulin. Too much insulin and there's the risk of hypoglycemia; too little and hyperglycemia (high glucose levels) is the concern. Exubera is the only form of insulin where dosing accuracy is even in question; for that reason alone, it gets a below average grade. When you add in the fact that according to Pfizer's presentation to

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	Syringe	Insulin Pen	Insulin Pump	Inhaled
US Market Share of insulin using patients	77.5%	15%	7.5%	0%
Cost of device	22 cents	\$25 to \$35	\$6,000+ does not include annual supply costs which on average run \$1,400 per year	Undetermined
Reimbursement	Λ	Λ	B/C	D
Ease of Use	A-	A+	A	C
Dosing Accuracy	Λ	Λ	Λ	C
Portability	B	A+	A	C
Maintenance	Λ	Λ	B-	C
Education Required to use the device properly	A+	A+	C-	C-
Vanity Factor	Λ+	Λ+	B	D
Physician Follow Up	A	A	A	C

the FDA's advisory panel, less than 30% of the insulin is actually absorbed in the lungs, it's unknown what happens to the other 70%. Compounding the dosing accuracy issue is the fact that Exubera comes in two different blister packs, 1mg and 3mg. This only adds to the potential for user error, as not only do patients have to calculate the conversion rate to injectable units, the

possibility exists that the patient could mistakenly use a 3mg blister when only a 1mg is needed. None of these possibilities exist with the other insulin delivery systems.

Portability - Because insulin patients do venture outside their homes and short-acting insulin is taken with

each meal, the device must be portable. Here, too, the grade for the insulin pump is a bit misleading as the pump is attached to the patient 24/7/365. Both a syringe and insulin pen can be placed in a pants pocket. The pen scores a higher grade as the insulin is contained in a pre-filled cartridge unlike the syringe which requires the patient carry the vial of insulin along with the syringe. While the Exubera device is portable, its size, even in the non-expanded mode, would make it difficult for gentlemen to carry the device in a pants pocket.

Maintenance – Syringes and pens require no maintenance whatsoever. Although insulin pumps do not require much in the way of maintenance, users must change batteries every 30 days or so. Also, being a machine, there is the possibility of malfunction. The Exubera delivery device is supposed to be cleaned once a week and the release unit must be changed every two weeks. The more the patient must handle the device, the greater the chance of breakage.

Education Required to use the device properly – This category does not include the education required to understand insulin therapy, simply how to operate the device. For obvious reasons, syringes and pens get the highest marks. The patient only needs to know where his shooting zones are and how to fill a syringe. Once a patient understands insulin therapy, using a pump isn't that complicated. However, it would be a vast overstatement to say that learning how to use an insulin pump is easy. The same can be said about Exubera. The key concern here is teaching patients how to properly convert

Based on our assessment of Exubera and its delivery device, Diabetic Investor believes that early adaptors of Exubera will HURT, not help, future usage of the product. This is in sharp contrast to other “firsts” to market products which typically enjoy the advantage of no competition. Just as Diabetic Investor accurately predicted that the use of Byetta would accelerate after reports from early adopters came in, we see the exact opposite happening for Exubera. Typically, when a new therapy option becomes available, physicians do their own form of test marketing; that is, they prescribe this new therapy to patients they know will give them an accurate assessment of what it’s like to use the product. In the case of Byetta, the early positive reports from patients convinced physicians they should prescribe Byetta to a greater percentage of their patients. It should be noted that Byetta is injected twice daily, yet the positive aspects of the drug have overcome what many believed was an obstacle to its use.

blister units into injectable units.

Vanity Factor - The simple fact is that a majority of people with diabetes don't want it known that they have diabetes. Here, the grade was determined by how easy it would be to administer the insulin in a public setting without anyone else knowing. While there will always be patients who don't feel comfortable injecting their insulin in public and prefer to do so in a private setting such as a restroom, insulin shots can be taken without anyone knowing. With the exception of the OmniPod insulin pump which is wireless and completely unnoticed, conventional insulin pumps look like a pager. Diabetic Investor finds it difficult to believe that someone using the Exubera delivery device could do so in a public place without getting noticed.

Physician Follow Up – Grades were determined by the simple fact if the physician was required to do any follow-up tests after the patient started using the device. According to the Exubera label, “Assessment of pulmonary function is recommended after the first six months of therapy, and annually thereafter, even in the absence of pulmonary symptoms.”

This adds to the cost of Exubera in two ways. First there is the cost of the test itself, and the doctor visit required to perform the test. While there is patient follow up with other delivery methods, Diabetic Investor is not aware of any additional tests that need to be performed or listed in the labels for conventional insulin.

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While physicians may be pleased with the reduction in a patient's HbA1c level, Diabetic Investor suspects they will hear a fair amount of complaints because of the delivery device. One problem with the insulin pump market has always been the amount of patient education required by the physician. Insulin delivered on a continuous basis with an insulin pump requires more effort than insulin that is injected. Unfortunately, physicians are poorly reimbursed for patient education, which has created a barrier for greater pump acceptance.

Exubera will face this same hurdle and then some. In nearly every report written on Exubera, the target market for the product is poorly controlled Type 2 patients. The general theory is that although the adoption rate may be small in the type 2 market, i.e. in the Goldman analysis, 15% of type 2 patients, this translates into over 2 million patients, and assuming a \$4 per day cost, that would translate into a \$3 billion market opportunity. There are several reasons why this won't happen:

80% of the patients with diabetes are treated by a primary care physician who lacks the time and support staff

to properly educate patients in insulin therapy. It should also be noted that this lack of resources expands beyond just educating patients. Insulin using patients generate a higher call volume for physicians and require greater monitoring

For all the hype surrounding Exubera, one very simple fact remains: take away the fact that it's inhaled rather than injected and no one would even be paying attention. It doesn't work any better than injected insulin. More than likely it won't cost less than injected insulin. It's also likely it will not be reimbursed at the same level as injected insulin. Patients will still have to be educated on the use of insulin. Patients will still need to test their glucose levels. The delivery device can hardly be called easier to use and could actually turn out to be a deterrent to usage. So, just what is all the hype about?

than patients on oral medications. The fact of the matter is that medicine is a business and insulin using patients are not as profitable as those on orals.

Inhaled or injected insulin users need to test their glucose levels more frequently than patients taking oral medications. The average non-insulin using patient tests less than twice a day. Inhaling the insulin may save the patient from the "pain" of injections; it does not save them from the "pain" of glucose monitoring.

Given the option of initiating insulin

therapy or Byetta for their poorly controlled type 2 patients, Byetta offers clear advantages. Besides providing excellent control, progressive weight loss and simple dosing regimen, there is little risk of hypoglycemia for patients on Byetta. The risk of a hypoglycemic event should not be underestimated as one of the primary reasons why physicians do not prescribe insulin to their type 2 patient population.

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