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

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Without question, the most lucrative market in the diabetes sector is oral medications targeted at patients with type 2 diabetes. In the United States alone, there are nearly 14 million people diagnosed with type 2 diabetes. According to the Department of Health and Human Services, there are another 50 million Americans who have pre-diabetes who will likely develop full blown diabetes in the future. A market analyst sees sales of diabetes drugs, currently at \$12 billion, growing to over \$26 billion by 2011.

Although there are injectable drugs, such as Byetta from Amylin (NASDAQ:AMLN), that are targeted at the type 2 market, physicians prefer orals as their primary treatment option. One reason for this is that nearly 80% of the patients with diabetes are treated by their primary care physician and not a diabetes specialist. Primary care physicians lack the time and infrastructure to provide their diabetic patients with the education they so desperately need. These same physicians also prefer oral medications because they believe a patient will be more compliant with their therapy

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regimen. Additionally, patients on orals generate fewer follow up calls than those on insulin or Byetta.

Currently leading the way in this category are two drugs from the thiazolidinediones (TZDs) class of drugs. They are Avandia from GlaxoSmithKline (NYSE:GSK) and Actos marketed by Lilly (NYSE:LLY) made by Takeda. In 2005, combined sales of Avandia and Actos were nearly \$4 billion in the U.S. alone. While there are some differences between the drugs, most physicians see them as mirror images of each other. Both can be used as a stand alone therapy or in combination with other oral diabetes medications, such as metformin or sulfonylurea, both available as generics.

TZDs are generally well tolerated with the primary concern being fluid retention that could lead to congestive heart failure. Secondly, patients on TZDs tend to gain weight. TZDs are also effective at lowering A1C levels and, when used as monotherapy, do not have significant risk for hypoglycemia. Overall, the majority of physicians see the benefits of TZDs outweighing the potential risks.

TZDs will soon face some serious competition from a new class of drugs called dipeptidyl peptidase-IV (DPP4). Januvia™ from Merck (NYSE:MRK) received Food and Drug Administration (FDA) approval on October 17 and Galvus® from Novartis (NYSE:NVS) should receive approval in the next few weeks.

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Analysts are estimating that both drugs could reach blockbuster status with sales exceeding \$2 billion each.

Like the TZDs, many see Januvia and Galvus as mirror images of each other. In clinical trials, both have proven effective at lowering A1C; but, what has everyone truly excited about is the lack of adverse events associated with DPP4s. According to data released at the European Association for the Study of Diabetes (EASD) this past September, DPP4s side effect profile closely matched the placebo. The most common side effects for Januvia was a runny nose and sore throat, reported in less than 3% taking the drug.

At the same meeting, Novartis released data from a study comparing Galvus to the TZD rosiglitazone (Avandia) which showed comparable A1C reductions. Yet patients taking Galvus did not see weight gain and also experienced a lower incidence of edema (2.5% vs. 4.95%).

Neither Januvia nor Galvus have shown signs of causing hypoglycemia and both can be used as monotherapy or in combination with metformin and TZDs.

According to a survey conducted by Reuters Primary Research, 90% of primary care providers said they intend to use Januvia and Galvus, while 95% of endocrinologists said they intend to use them.

Based on the effectiveness of DPP4s, a favorable side effect profile, physicians high awareness of both drugs along with their willingness to use the drugs, and a growing type 2 patient population, it is easy to see why expectations are running at such high levels. Add in the fact that Merck and Novartis have

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the resources to reach physicians and patients, and this could be one of the biggest drug launches of all time.

The sales teams from Merck and Novartis are gearing up to do battle in what looks to be an all out fight for market supremacy. At first glance, some believe Merck has more at stake with Januvia than Novartis with Galvus, as the company desperately seeks to put the Vioxx disaster behind them. With its blockbuster potential, many see Januvia as the homerun Merck needs.

While expectations are high within the Merck sales force, there are already grumblings from within that the company is spending too much time on metrics and not letting the sales people do their job. Even before Januvia was officially approved by the FDA, Merck reps were aggressively touting Januvia, telling physicians Januvia is the oral version of Byetta.

On the other hand, Merck lacks experience in the diabetes market while Novartis has been selling another type 2 oral medication, Starlix. Diabetic Investor does see this as an advantage,

but isn't sure this is enough of an edge to push them past Merck. For their part, Novartis sales people are taking an approach commonly used by politicians as they are attacking the credibility of their opponent. These reps know physicians have been burned by Merck in the past (can you say Vioxx?), and are mentioning this whenever possible. The fact of the matter is Vioxx is Merck's Watergate.

Not to be left out of the mix are Glaxo, Lilly and Amylin. Each company has a stake in this market and won't sit idly by and let Merck or Novartis steal their thunder.

With billions at stake, the games have already begun from all sides, starting with recent published reports that implied patients using Byetta are experiencing serious adverse events. In one report by Bear Stearns it stated, "Shortly after the ADA, concerns that Byetta might cause pancreatitis emerged." The report concluded by stating, "Our literature analysis reveals several hints about potential 'plausible biology' which could help explain the serious adverse events in the AERS database. We think that the mechanism we highlighted in this note applies only to Ex-4 and should not extend to human GLP-1 analogues."

Next was a report on sermo.com, a web-site that came on line at the beginning of October, saying that Byetta was associated with "sudden death" in 50 patients.

As Diabetic Investor stated back on October 4th in response to the Bear Stearns report, "Diabetic Investor sees the report as a clear attempt by the short community to create a dark cloud over Amylin's truly bright future". While we are not really sure just what

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plausible biology is or how you can compare Byetta to Lantus or Lyrica, there are some things we are sure of:

Byetta is not some new drug that just hit the market. Byetta has been on the market for nearly 18 months and is used by nearly 500,000 patients.

Byetta prescription growth continues to accelerate.

While there are adverse events associated with Byetta, in the many interviews Diabetic Investor has done with physicians who prescribe the drug and patients who use the drug, pancreatitis has never come up.

In late September, a European Commission medical panel issued a positive opinion recommending approval of exenatide for the treatment of type 2 diabetes.

All clinical evidence to date shows Byetta to be safe and effective.

Some may recall when Rezulin, an oral medication for type 2 patients, was pulled from the market due to liver toxicity problems. There was overwhelming evidence and the issue was brought to the FDA's attention by the medical community.

If there is a link between Byetta usage and pancreatitis, one would think that we would see some concrete evidence and not mere innuendo. Surely the many physicians who prescribe Byetta would stop or at least slow down the number of patients they place on Byetta. There is no evidence of this as prescription growth continues to accelerate.

Diabetic Investor sees Bear Stearns

The accusation posted on sermo.com also fails to pass the smell test. Diabetic Investor has not found any evidence whatsoever that Byetta was associated with any 'sudden deaths', let alone 50 such events. With nearly 500,000 patients taking Byetta, any such adverse event would have surely surfaced. There is no way physicians would continue to prescribe Byetta if such reports were accurate. Diabetic Investor not only believes this posting was an attempt by the short community to lower Amylin's share price, but it is also an example of the worst journalism the internet has to offer.

playing to investors' fears that the FDA has approved another potentially dangerous drug. And it is possible that Diabetic Investor is wrong about Byetta and Amylin. Based on the facts, we remain firm in our belief that Amylin is the most valuable property in the diabetes sector. It will take real and credible evidence, not rumor and innuendo, to change our mind.

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About the same time Byetta came under attack, a report was released by The Cochrane Library (a quarterly publication of medicine reviews from the nonprofit Cochrane Collaboration), that found no long-term benefit to taking Actos. According to the lead author Bernard Richter, M.D., assistant professor in the department of endocrinology, diabetes and rheumatology at Heinrich-Heine University in Düsseldorf, Germany, "Our results showed that published scientific stud-

ies of at least 24 weeks of pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects and health-related quality of life are positively influenced by this drug." Dr. Richter went on to state, "Until new evidence becomes available, the benefit-risk ratio of pioglitazone in type 2 diabetes mellitus remains unclear."

John Buse, M.D., director of the Diabetes Care Center at the University of North Carolina School of Medicine, responded to the report stating. "I am fairly certain that we are better off with pioglitazone than without it. We do not have proof but a great deal of signal that the benefits outweigh the risks. There are more data to come. The authors of the review are not incorrect in their assessments, but there is just not enough long-term data available in the literature to be certain of the benefits whereas the risks are much easier to assess."

Not to be outdone, Glaxo was the first company to publicly talk about a potential dark cloud forming over both Januvia and Galvus. During the question and answer session of their third quarter conference call, the company acknowledged that there is some evidence that long-term use of a DPP4 may cause cancer. Glaxo is one of several companies that has a DPP4 in their pipeline.

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Glaxo may have been the first company to acknowledge this in public, but they are not alone in concerns over long term use of DPP4s. In a study published by ScienceDirect entitled, DPPIV inhibitors extend GLP-2 mediated tumor promoting effects on intestinal cancer cells by K. Masur, F. Schwartz, F. Entschladen, B. Niggemann and K.S. Zaenker, the authors concluded, "Considering elevated GLP-2 levels due to treatment with DPPIV inhibitors, a higher proliferation rate will be an advantage for all cells with respect to tumor progression. Additionally, cell lines with metastatic potential will be more active in cell migration, even when GLP-2 itself does not induce metastasis. Furthermore, if there is a trend in down-regulating CD26/DPPIV activity in cancer cells *per se*, the use of DPPIV inhibitors to treat diseases like diabetes, short bowel syndrome or ulcerative colitis, where a long time treatment is indispensable, would amplify those tumor promoting effects. With regards to patients with increased gastrointestinal cancer susceptibility, long time investigations should be performed to estimate the risk of a prolonged GLP-2 treatment and/or the use of DPPIV inhibitors for cancer development and progression."

Some physicians, initially excited by Januvia and Galvus, have tempered their enthusiasm as these concerns have become more public. This would not be the first time the FDA has

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approved a drug for the treatment of type 2 diabetes that eventually turned out to be unsafe or have serious adverse events; think Rezulin. With a host of drugs to choose from for the treatment of type 2 diabetes, it's not like Januvia or Galvus are the only options available. This is especially true when you consider that Januvia or Galvus don't work any better than currently available therapies; in nearly every clinical trial the drugs worked as well as, not better than, TZDs or metformin. The big selling point with both drugs is the apparent lack of adverse events and no weight gain.

While the Masur study does not show a straight line between using a DPP4 and getting cancer, many believe this issue deserves further study. Some have gone as far as stating, off the record, that the FDA was too quick

with their approval of Januvia or they should have at least required some mention of this possibility in the Januvia label. Diabetic Investor sees this as a problem for Merck as the Vioxx situation remains fresh in everyone's mind.

The bottom line here is this fight for the type 2 market is just beginning and everyone involved is a heavyweight contender. Merck, Novartis, Glaxo, Lilly and Amylin better be prepared to mix it up. Januvia hasn't even hit the physicians' offices yet and punches are already being thrown. Based on what Diabetic Investor has seen so far, this will be anything but a clean fight.

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