BUSINESS & REGULATORY NEWS

Amylin's pramlintide best of bad bunch of diabetes drugs

When Amylin (San Diego, CA) announced ambiguous results in August from two phase III trials of its synthetic amylin analog, pramlintide, investors sold stock and wiped over 40% off the value of the company. That apparent bad news was followed in September by Genentech's (South San Francisco, CA) announcement that it will stop further development of recombinant insulin-like growth factor-1 (IGF-1) as an adjunct to insulin, despite positive data reported a few months ago. In neither case did the bad clinical news mean that the drugs were bad, however. Indeed, there is strong evidence that both worked.

Diabetes is an important and serious disease with an estimated 100 million sufferers worldwide. Over 90% of patients have type 2, or adult-onset, diabetes, in which the β-cells of the pancreas are progressively destroyed. The disease is particularly prevalent in the developed nations and it places disproportionate demands on health-care services. Estimates made in 1992 indicate that the 3.1% of the US population that has diabetes consumed 11.9% of health expenditures.

Genentech and Amylin were both developing drugs for the 80% of diabetics whose disease was poorly controlled by insulin. Diabetes that is poorly controlled leads to abnormally high levels of glucose in the blood, a condition that greatly increases the risk of succumbing to the circulatory and nervous-system complications of diabetes. One of the key indicators of glucose control is the presence of glycated proteins in the blood. A level of glycated hemoglobin of 8% or above is used by the American Diabetic Association (ADA; Alexandria, VA) as a definition of poor glucose control. A 10% reduction in glycated hemoglobin correlates closely with a 40–45% reduction in the risk of complications.

At the American Diabetes Association Meeting in June, which took place in June, Genentech showed data indicating that IGF-1 lowered blood sugar and worked synergistically with insulin to increase insulin sensitivity. It also did not promote weight gain.

Genentech's decision not to proceed with IGF-1 in diabetes stemmed not from these clinical outcomes, but from recent discussions with the US Food and Drug Administration (FDA; Bethesda, MD). One of the complications of diabetes is retinopathy, which can lead to blindness. While there was no evidence indicating that IGF-1 worsened or hastened retinopathy, FDA had expressed concerns that, as a growth factor, IGF-1 might contribute to this complication. It would have required Genentech to undertake expensive, long-term trials. Since Genentech is already pursuing applications for IGF-1 in neurological and other metabolic indications, it decided to drop the diabetes program.

Amylin's clinical trial results, on the other hand, sent Wall Street into a spin because the trials were poorly designed and produced ambiguous data.

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Amylin's pramlintide (and the natural hormone, amylin) works by slowing the movement of food-derived glucose into the blood and, used in combination with insulin, should theoretically provide better glucose control. The idea behind its trials in type 1 and type 2 diabetes patients was to compare insulin alone with insulin plus pramlintide as a method to control glucose levels. The company wanted to demonstrate that pramlintide could reduce glycated hemoglobin levels by 1%. The problem with the trials, however, was that the investigators seemed to take every step possible to obscure their positive results. They started off by admitting some patients to the trials whose glycated hemoglobin levels were below the 8% level defined by the ADA as representing "poor glucose control." They then hurried to established a baseline of insulin usage; for a trial that was to last 6–12 months, they required patients to demonstrate only a week of stable insulin dosage.

Having established a shaky baseline, problems arose because patients blood sugar levels were unblinded and those on placebo, who often needed more insulin than their baseline, were given it. Patients given pramlintide frequently needed less insulin than their baseline level, and it was reduced. Then, three months into the type 1 trial, some of the patients who had not achieved the required reduction in glycated hemoglobin had their dose of pramlintide doubled.

Despite these missteps, both trials produced positive data. In the type 1 trial, 20% of patients had achieved the 1% reduction in glycated hemoglobin. Patients had significantly improved glucose control without increased risk of hypoglycemia, and also had reductions in body weight and improved cholesterol profiles. Overall, the treated group showed a 0.3% reduction in glycated hemoglobin after 12 months compared to the placebo group. Patients experienced a statistically significant weight loss and an improved cholesterol profile.

Michael King, an analyst at Vector Securities (Deerfield, IL) pointed out that those patients with poor glucose control (8% glycated hemoglobin as defined by ADA) showed reductions in glycated hemoglobin of 0.4%. Moreover, for a subset of those patients in whom insulin dosing remained constant over 12 months the reduction was 0.66%. King also noted that nearly twice as many pramlintide patents had reduced glycated hemoglobin levels as did those on placebo—6% versus 29%.

There were also positive indications in the trial involving type 2 diabetes patients. Again, the best results were seen in those patients who both met the ADA definition of poor glucose control and maintained their insulin dosing. Average reduction in glycated hemoglobin reached 0.7–0.85%, depending on the dose. The main difficulty in interpreting those results, however, was that the variable dosing regimens meant that few of the outcomes were statistically significant.

Amylin is still running four pivotal trials involving 1,800 diabetes patients. It has revised its trial design to remove both the entry anomalies and the in-trial insulin dosage variation. These will be completed in 1998. Significantly, Amylin's partner, Johnson & Johnson (New Brunswick, NJ), which has invested about $117 million so far in pramlintide's development, is still supporting the program.

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