



BYETTA[®] (exenatide) injection

The discovery and development of a unique treatment for type 2 diabetes

Increasing Demand for Treatment Options

The incidence of diabetes is increasing at an alarming rate and is the fifth deadliest disease in the United States. Along with the prevalence of obesity and longer lifespan, the number of people with type 2 diabetes, which results from the body's inability to make enough or properly use insulin, is growing. Alongside, the need for alternative and novel therapies to treat the array of metabolic abnormalities resulting from and associated with type 2 diabetes has increased. While diet and exercise are the foundation of treating type 2 diabetes, oral medications are often required to adequately control blood sugar. Oral medications may be used alone or in combination. As diabetes progresses and the oral agents can no longer control patients' glucose levels, insulin may be added in an effort to maintain control.

However, two companies – Amylin Pharmaceuticals, Inc. and Eli Lilly and Company – saw an opportunity for a new approach for treating type 2 diabetes. After years of research and planning, BYETTA[®] (exenatide) injection is the world's first type 2 diabetes treatment in a new class of drugs known as incretin mimetics.

A Mentor's Early Encouragement

As a research fellow working in the laboratory of Nobel Prize winner Dr. Rosalyn Yalow at the Bronx Veterans Affairs (VA) Medical Center in New York, a young endocrinologist named Dr. John Eng set his sights on discovering novel hormones. Dr. Yalow, who won the Nobel Prize for inventing the testing technique called the radioimmunoassay, encouraged the young researcher to work hard, think big and make important discoveries.

The Global Hunt for Hormones

In the late '70s and early '80s, scientists from the NIH as well as Belgium and the Karolinska Institute in Sweden uncovered several other new hormones that might play a role in digestive and metabolic processes. These discoveries ignited a flurry of research in labs throughout the world, including Dr. Eng's. The race was to understand how these new peptides worked, their purpose and the location of their hormone receptors within the human body.

Dr Eng's Breakthrough

Dr. Eng began further investigation into a large family of hormones. He also developed an assay based on a chemical marker to screen for novel peptides. Using this assay on a sample of dried Gila monster (*heloderma suspectum*) saliva, Dr. Eng observed two "peaks" of concentrated activity – one large peak and one small peak. When he determined the structure of the peptides responsible for the peaks, he discovered that one of the peaks contained a new peptide hormone, which he named exendin-4. Exendin-4 is now known as exenatide, the active ingredient in BYETTA.

Dr. Eng found that exendin-4 had important glucose-lowering effects making it potentially useful as a treatment for type 2 diabetes. It turned out that exendin-4 shares many of the same properties as glucagon-like peptide-1 (GLP-1), which is a gut hormone that plays an important role in regulating glucose in humans. Both exendin-4 and GLP-1 enhance the body's ability to release insulin only in response to elevated levels of glucose, thereby reducing the likelihood that glucose levels will be too high or too low. But there is also a very important difference between the two molecules. GLP-1 is metabolized in less than two minutes upon administration, a fact that had repeatedly frustrated attempts to develop GLP-1 into a viable treatment for diabetes. In contrast, exendin-4 has much longer activity, lasting for hours.^{1,2,3} This trait gave the compound significant value as a potential therapeutic agent.

Beyond the Discovery – Patent and Licensing

After Dr. Eng discovered that exendin-4 could be used to stimulate insulin secretion in various models, he spent two years and \$8,000 of his own money to obtain a patent on this new use. He received a United States patent in 1995, and began meeting with pharmaceutical companies to try to interest them in licensing and further developing the compound.

Dr. Eng presented his findings on the long-acting actions of exendin-4 in diabetic mice at the annual meeting of the American Diabetes Association in June of 1996. Scientists from various pharmaceutical companies expressed interest in learning more, but it was Amylin who jumped at the opportunity. Within months of seeing the poster at the ADA, Amylin licensed exendin-4 from Dr. Eng and began further research into the compound as a potential treatment for type 2 diabetes.

Amylin's scientists discovered that the glucose-lowering effect of exendin-4 was the result of multiple mechanisms of action. In addition to enhancing the body's ability to produce insulin only when needed, it suppressed the release of the blood-sugar raising hormone glucagon, slowed the rate of nutrient absorption, promoted satiety, and reduced food intake. Amylin completed the Phase 1 clinical studies in 1998 and filed an investigational new drug application with the Food and Drug Administration in 1999. In September 2002, Eli Lilly and Company signed a collaboration agreement with Amylin Pharmaceuticals, joining in the effort to develop and commercialize a synthetic version of the exendin-4 compound, which is now known as exenatide.

"Scientific innovation requires asking the right questions and working hard with a guiding hypothesis." said Dr. Eng. By asking the right questions at the right time, Dr. Eng fulfilled his mentor's call to think big and make discoveries. This discovery has considerable promise in the treatment and understanding of human disease.

BYETTA® Breaks Through

BYETTA was much anticipated, creating significant scientific and media impact at the ADA's annual meeting in June of 2004, eight years after Dr. Eng's original abstract. A New Drug Application (NDA) was submitted to the U.S. Food and Drug Administration (FDA) in late June 2004 and approved in the spring of 2005.

About BYETTA®

BYETTA® (exenatide) injection was approved by the FDA on April 28, 2005 as adjunctive therapy to improve blood sugar control in patients with type 2 diabetes who have not achieved

adequate control on metformin and/or a sulfonylurea, two common oral diabetes medications. BYETTA was then approved by the FDA on December 22, 2006 as an add-on therapy to a thiazolidinedione (TZD), another common diabetes medication. BYETTA (pronounced bye-A-tuh), the trade name for exenatide, is the first in a new class of medicines known as incretin mimetics.

BYETTA improves blood sugar control by lowering both postmeal and fasting glucose levels leading to better long-term control as measured by hemoglobin A1C. BYETTA does this through several actions, including the stimulation of insulin secretion only when blood sugar is high and by restoring the first-phase insulin response, an activity of the insulin-producing cells in the pancreas that is lost in patients who have type 2 diabetes. Most patients in the long-term BYETTA clinical studies also experienced reductions in weight.

Important Safety Information for BYETTA® (exenatide) injection

BYETTA improves glucose (blood sugar) control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a thiazolidinedione. BYETTA is not a substitute for insulin in patients whose diabetes requires insulin treatment. BYETTA is not recommended for use in patients with severe problems with the stomach or food digestion, or those who have severe kidney disease. Before using BYETTA, patients should tell their healthcare provider if they are pregnant, plan to become pregnant, or are breastfeeding. BYETTA has not been studied in children.

When BYETTA is used with a medicine that contains a sulfonylurea, hypoglycemia (low blood sugar) is a possible side effect. To reduce this possibility, the dose of sulfonylurea medicine may need to be reduced while using BYETTA. Other common side effects with BYETTA include nausea, vomiting, diarrhea, dizziness, headache, feeling jittery, and acid stomach. Nausea is most common when first starting BYETTA, but decreases over time in most patients. BYETTA may reduce appetite, the amount of food eaten, and body weight. No changes in dose are needed for these side effects. These are not all the side effects with BYETTA. A healthcare provider should be consulted about any side effect that is bothersome or does not go away.

For complete safety profile and other important prescribing considerations, visit www.BYETTA.com.

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References:

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2. Gedulin B, Lawler R, Jodka C, Young A 1997 Amylin inhibits pentagastrin-stimulated gastric acid secretion: comparison with glucagons-like peptide-1 and exendin-4 (Abstract). *Diabetes* 46:188A, 1997
3. Nishizawa M, Nakabayashi H, Kawai K, Ito T, Kawakami S, Nakagawa A, Nijima A, Uchida K 2000 The hepatic vagal reception of intraportal GLP-1 is via receptor different from the pancreatic GLP-1 receptor. *J Auton Nerv Syst* 80:14-21, 2000

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