

BYETTA® (exenatide) Injection The Discovery and Development of the First GLP-1 Receptor Agonist for Treatment of Type 2 Diabetes

In the late 1970s and early 1980s, scientists discovered several new peptide hormones that play a role in digestive and metabolic processes. These discoveries ignited a flurry of research in labs throughout the world to understand how these new peptides worked, their purpose, and the location of their hormone receptors within the human body.

The Discovery of Exendin-4

One researcher who became interested in these hormones was a young endocrinologist named Dr. John Eng, who began further investigation into a large family of hormones and developed an assay, a procedure for testing and measuring the activity of a drug, 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 large and small “peaks” of concentrated activity. 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 (exenatide) injection.

Dr. Eng found that exendin-4 had important glucose-lowering effects, making it potentially useful as a treatment for type 2 diabetes. Exendin-4 shares many of the same properties as glucagon-like peptide-1 (GLP-1), 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 low¹; however, there is an important difference between the two molecules. GLP-1 is metabolized in less than two minutes upon administration, which has frustrated attempts to develop GLP-1 into a viable treatment for diabetes.¹ In contrast, exendin-4 has much longer activity, lasting for hours.² 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, which he received in 1995. 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 (ADA) in June 1996. Scientists from various pharmaceutical companies expressed interest in learning more, but it was Amylin Pharmaceuticals, Inc. that jumped at the opportunity. Within months of seeing the poster at the ADA, Amylin licensed exendin-4 and began further research into the compound as a potential treatment for type 2 diabetes.

Unique Mechanism of Action of Exenatide

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, and reduced food intake. Amylin completed the Phase 1 clinical studies in 1998 and filed an investigational new drug

application with the U.S. Food and Drug Administration in 1999. In September 2002, Eli Lilly and Company signed a collaboration agreement with Amylin, joining in the effort to develop and commercialize a synthetic version of the exendin-4 compound.

BYETTA® Breaks Through

BYETTA was much anticipated, creating significant scientific and media impact at the ADA's annual meeting in June 2004, eight years after Dr. Eng's original abstract. Shortly after, a New Drug Application was submitted to the FDA. BYETTA was approved for marketing in the United States in April 2005 as adjunctive therapy to improve glycemic control in patients with type 2 diabetes taking metformin, a sulfonylurea, or a thiazolidinedione but who have been unsuccessful at controlling their blood sugar levels. In 2009, the FDA approved an expanded indication for BYETTA as a stand-alone therapy (monotherapy) along with diet and exercise.

BYETTA has a proven history with 4 years on the market, over 10 million prescriptions written,³ and 6.5 years of clinical experience. Since market availability in June 2005, more than 1 million patients have used BYETTA.⁴ BYETTA offers powerful, sustained A1C reductions with potential weight loss. BYETTA is not a weight-loss product.

Acknowledging the approach of treating diabetes with glucose control therapies that promote weight loss without increasing hypoglycemia, the ADA and the European Association for the Study of Diabetes (EASD) updated treatment guidelines at the end of 2008 to include BYETTA. The revised treatment guidelines introduced BYETTA as the only new addition, placing it in a more prominent position and suggesting it as appropriate treatment in patients for whom both weight management and hypoglycemia are a concern. In addition, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) in October 2009 issued a new type 2 diabetes algorithm in which GLP-1 agonists are recommended for use earlier in the treatment continuum based on effectiveness and overall safety profile.⁵

About BYETTA® (exenatide) injection

BYETTA® is the first FDA-approved GLP-1 receptor agonist for the treatment of type 2 diabetes. BYETTA exhibits many of the same effects as the human incretin hormone glucagon-like peptide-1 (GLP-1). GLP-1 improves blood sugar after food intake through multiple effects that work in concert on the stomach, liver, pancreas and brain.

BYETTA is an injectable prescription medicine that may improve blood sugar (glucose) control in adults with type 2 diabetes mellitus, when used with a diet and exercise program. BYETTA is not insulin and should not be taken instead of insulin. BYETTA is not recommended to be taken with insulin. BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis.

BYETTA provides sustained A1C control and low incidence of hypoglycemia when used alone or in combination with metformin or a thiazolidinedione, with potential weight loss. BYETTA is not a weight loss product. BYETTA was approved in April 2005 and has been used by more than 1 million patients since its introduction. For full prescribing information, visit www.BYETTA.com.

Important Safety Information for BYETTA

Based on post-marketing data, BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. The risk for getting low blood sugar is higher if BYETTA is taken with another medicine that can cause low blood sugar, such as a sulfonylurea. BYETTA should not be used in people who have severe kidney problems, and should be used with caution in people who have had a kidney transplant. Patients should talk with their healthcare provider if they have severe problems with their stomach, such as delayed emptying of the stomach (gastroparesis) or problems with digesting food. Severe allergic reactions can happen with BYETTA.

The most common side effects with BYETTA include nausea, vomiting, diarrhea, dizziness, headache, feeling jittery, and acid stomach. Nausea most commonly happens when first starting BYETTA, but may become less over time.

These are not all the side effects from use of BYETTA. A healthcare provider should be consulted about any side effect that is bothersome or does not go away.

For Prescribing Information and Medication Guide, visit www.BYETTA.com.

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References:

1. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab.* 2004; 287.
2. Young AA, Gedulin BR, Bhavsar S, Bodkin N, Jodka C, Hansen B, Denaro M. Glucose-lowering and insulin-sensitizing actions of exendin-4. Studies in obese diabetic (ob/db/db) mice, diabetic fatty Zucker rats, and diabetic Rhesus monkeys (*Macaca mulatta*). *Diabetes* 48:1026-1034, 1999.
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