



The Discovery and Development of BYETTA® (exenatide) Injection and BYDUREON™ (exenatide extended-release for injectable suspension)

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 and BYDUREON™ (exenatide extended-release for injectable suspension).

Dr. Eng found that exendin-4 had 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 low; 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 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 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 American Diabetes Association meeting, Amylin licensed exendin-4 and began further research into the compound as a potential treatment for type 2 diabetes.

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, delayed gastric emptying 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 (FDA) in 1999.

BYETTA Breaks Through

BYETTA was much anticipated, creating significant scientific and media impact at the annual meeting of the American Diabetes Association 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 in the U.S. in April 2005 as adjunctive therapy to improve glycemic control in patients with type 2 diabetes taking certain oral medications but who have been unsuccessful at controlling their blood sugar levels. In 2009, the FDA approved an expanded use for BYETTA as a stand-alone therapy (monotherapy) along with diet and exercise. It was approved as an add-on therapy to insulin glargine in 2011, expanding the indication for the use of BYETTA across the continuum of type 2 diabetes care.

BYETTA has a proven history, with millions of prescriptions written. Since market availability in June 2005, more than 1.8 million patients have used BYETTA in nearly 80 countries worldwide. BYETTA provides sustained A1C control 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 American Diabetes Association and the European Association for the Study of Diabetes (EASD) consensus panel updated treatment guidelines at the end of 2008 to include the GLP-1 receptor agonist class. 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) consensus panel in October 2009 issued a new type 2 diabetes consensus treatment algorithm in which GLP-1 receptor agonists are recommended for use earlier in the treatment continuum based on effectiveness and overall safety profile.³

BYDUREON: The First Once-Weekly Treatment for Type 2 Diabetes

Nearly seven years after BYETTA was approved by the FDA, the second type 2 diabetes treatment based on exendin-4 became available. BYDUREON received its first regulatory approval in June 2011 in the EU, and it was approved in the U.S. in January 2012 to improve glycemic control in adults with type 2 diabetes. The approval of BYDUREON was based on data from the DURATION series of clinical studies, as well as clinical and post-marketing experience with BYETTA.⁴

BYDUREON is the first and only once-weekly treatment for type 2 diabetes. BYDUREON provides continuous glycemic control in a single weekly dose. BYDUREON uses proprietary technology for long-acting medications developed by Alkermes plc to provide a controlled release of exenatide.

About BYETTA® (exenatide) injection

BYETTA was the first glucagon-like peptide-1 (GLP-1) receptor agonist to be approved by the FDA for the treatment of type 2 diabetes. BYETTA exhibits many of the same effects as the human incretin hormone 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. It can also be used with metformin, a sulfonylurea, a thiazolidinedione or Lantus® (insulin glargine), which is a long-acting insulin.

BYETTA is not insulin and should not be taken instead of insulin. BYETTA should not be taken with short- and/or rapid-acting insulin. BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis. BYETTA has not been studied in patients with a history of pancreatitis. Other antidiabetic therapies should be considered for these patients.

BYETTA provides sustained A1C control with potential weight loss (BYETTA is not a weight-loss product). BYETTA was approved in the U.S. in April 2005 and in Europe in November 2006 and has been used by more than 1.8 million patients since its introduction. See important safety information below. Additional information about BYETTA is available at www.BYETTA.com.

Important Safety Information for BYETTA® (exenatide) injection

Based on post-marketing data, BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Patients should be observed for signs and symptoms of pancreatitis after initiation or dose escalation of BYETTA.

The risk of getting low blood sugar is higher if BYETTA is taken with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. The dose of sulfonylurea or insulin may need to be lowered while BYETTA is used. BYETTA should not be used in people who have severe kidney problems and may cause or worsen problems with kidney function, including kidney failure. 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. Antibodies may develop with use of BYETTA. Patients who develop high titers to exenatide could have worsening or failure to achieve adequate glycemic control. Severe allergic reactions can happen with BYETTA. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

The most common side effects with BYETTA include nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, acid stomach, constipation and weakness. 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 additional important safety information about BYETTA, please see the full Prescribing Information (www.BYETTA.com/pi) and patient Medication Guide (www.BYETTA.com/mg).

About BYDUREON™ (exenatide extended-release for injectable suspension)

BYDUREON, previously known as exenatide once weekly, is the first and only once-weekly medicine to be approved by the FDA for the treatment of type 2 diabetes. BYDUREON works with the body to help make its own insulin when needed, providing continuous glycemic control with just one dose per week. Each dose of BYDUREON is made up of biodegradable microspheres that provide a controlled release of exenatide throughout the week.

BYDUREON is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise. BYDUREON is not recommended as the first medication to treat diabetes.

BYDUREON is a long-acting form of the medication in BYETTA® (exenatide) injection so both drugs should not be used together. BYDUREON is not insulin and should not be taken instead of insulin. BYDUREON is not for people with type 1 diabetes or people with diabetic ketoacidosis. BYDUREON is not recommended for use in children. It is not known if BYDUREON is safe and effective in people with a history of pancreatitis or severe kidney problems. See important safety information below. Additional information about BYDUREON is available at www.BYDUREON.com.

Important Safety Information for BYDUREON™ (exenatide extended-release for injectable suspension)

In animal studies, BYDUREON caused rats to develop tumors of the thyroid gland. Some tumors were cancers. It is not known if BYDUREON causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in people. BYDUREON should not be used if there is a personal or family history of MTC or Multiple Endocrine Neoplasia syndrome type 2.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Patients should be observed for signs and symptoms of pancreatitis after initiation of BYDUREON.

The risk of getting low blood sugar is higher if BYDUREON is taken with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of sulfonylurea may need to be lowered while BYDUREON is used. BYDUREON should not be used in people who have or had severe kidney problems and may cause or worsen problems with kidney function, including kidney failure. 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. Antibodies may develop with use of BYDUREON, which may lead to worsening or failure to achieve adequate glycemic control. Severe allergic reactions can happen with BYDUREON. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

The most common side effects with BYDUREON include nausea, diarrhea, headache, vomiting, constipation, itching at injection site, a small bump (nodule) at the injection site, and indigestion. Nausea most commonly happens when first starting BYDUREON, but may become less over time.

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

For additional important safety information about BYDUREON, please see the full Prescribing Information (www.BYDUREON.com/pi) and patient Medication Guide (www.BYDUREON.com/mg).

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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.

³ Rodbard H, Jellinger P, Davidson J, Einhorn D, Garber A, Grunberger G, Handelsman Y, Horton E, Lebovitz H, Levy P, Moghissi E, Schwartz S. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control. *Endocrine Practice.* 2009; 15(6): 540-559.

⁴ Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Dongliang Z, Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised open-label, non-inferiority study. *The Lancet.* 2008;372,9645:1240–1250.