

The Role of GLP-1 in the Treatment of Type 2 Diabetes

GLP-1 Overview

Incretin hormones are those that cause an increase in the amount of insulin released from beta cells following ingestion of a meal.¹ In the pancreas, incretin hormones act to increase glucose-dependent insulin secretion from beta cells²; this action helps to ensure an appropriate insulin response after eating.¹ The most well-characterized incretin hormone is glucagon-like peptide-1 (GLP-1), which is considered to be the most important incretin released by the gut into the bloodstream in response to food.³ In addition to its effects on insulin secretion after eating, GLP-1 also has additional effects that can help in the management of diabetes.³⁻⁵

The primary function of GLP-1 is to enhance insulin secretion only in the presence of elevated blood sugar (glucose) concentrations.³ GLP-1 also suppresses the release of glucagon from the pancreas.⁴ Glucagon stimulates glucose release from the liver⁶; so decreasing the amounts of glucagon helps to improve glucose control.^{3,4} It is postulated that GLP-1 acts in the brain to reduce appetite⁴ and in the stomach to slow the rate of gastric emptying so that nutrients are not absorbed too quickly into the bloodstream.⁵ In addition, GLP-1 has been shown to improve acute beta-cell function in humans.³

In short, GLP-1 exerts multiple effects that contribute to the maintenance of glucose homeostasis:³⁻⁵

- Enhances glucose-dependent insulin secretion
- Suppresses inappropriate glucagon secretion
- Reduces appetite, leading to reduction of food intake
- Regulates the rate of gastric emptying, so that nutrients are not absorbed as quickly into the bloodstream

GLP-1 and Type 2 Diabetes

People with type 2 diabetes often have inappropriately elevated levels of glucagon.⁷ The elevated glucagon, which is produced in pancreatic alpha cells, causes the liver to release an excessive amount of glucose into the bloodstream, which then contributes to high blood glucose seen in type 2 diabetes.⁸ Many people with diabetes may also have an accelerated rate of gastric emptying, which leads to increased nutrient delivery to the intestine resulting in an abnormally rapid rise in glucose following a meal.⁹ The levels and actions of GLP-1 appear to be deficient in many people with type 2 diabetes, thus creating an opportunity for antidiabetes medications that act directly on the GLP-1 receptor or inhibit the breakdown of GLP-1 in the bloodstream.⁷

GLP-1 Antidiabetes Treatments

Native human GLP-1 is rapidly inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme,¹⁰ resulting in an extremely short half-life—approximately two minutes—in the blood.³ The short half-life presents a challenge for its use as a therapeutic agent given the constraint around duration of action.¹¹ However, two treatment approaches have been developed to increase the amount of circulating GLP-1: GLP-1 receptor agonists and DPP-4 inhibitors.¹²

GLP-1 Receptor Agonists

Agonist versions of GLP-1 that have a longer half-life or are more potent can have therapeutic advantages.¹¹ An agonist is a molecule, such as a drug or a hormone, which binds to a receptor of a cell and triggers a response by that cell.¹³ A GLP-1 receptor agonist

binds to and activates the human GLP-1 receptor, the subsequent action of which leads to acutely enhanced beta-cell function and other effects, resulting in improved glucose control.³ Also, GLP-1s have the potential for weight loss,* unlike the weight gain that is commonly associated with insulin therapy and many oral diabetes medications.¹⁴

Recognizing the unique benefits of GLP-1s, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) updated the consensus treatment algorithm in late 2008 to include this class of antidiabetes medications for patients in whom either hypoglycemia is a concern or promotion of weight loss is a consideration.¹⁵ 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.¹⁶

BYETTA® (exenatide) injection is the first FDA-approved GLP-1 receptor agonist for the treatment of type 2 diabetes. BYETTA has consistently demonstrated multiple effects for people with type 2 diabetes by mimicking many of the actions of GLP-1.

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 has been shown to have the following five distinct benefits:¹⁷⁻¹⁸

- Enhances glucose-dependent insulin secretion
- Restores first-phase insulin response
- Suppresses glucagon toward normal for reduced glucose output
- Slows accelerated gastric emptying
- Reduces appetite and food intake*

BYETTA has a proven history: 4 years on the market, over 10 million prescriptions written,¹⁹ and 6.5 years of clinical experience. Since market availability in June 2005, more than 1 million patients have used BYETTA.²⁰

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.

*BYETTA is not indicated for the management of obesity, and weight change was a secondary endpoint in clinical trials.

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References:

1. Drucker D. The role of gut hormones in glucose homeostasis. *J Clin Invest.* 2007; 117: 24-32.
2. Nauck M, Stockmann F, Ebert R, et al. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. *Diabetologia.* 1986; 29(1): 46-52.
3. 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.
4. Zander M, Christiansen A, Madsbad S, Holst JJ. Additive Effect of Glucagon-Like Peptide 1 and Pioglitazone in Patients with Type 2 Diabetes. *Diabetes Care.* 2004; 27: 1910-1914.
5. D'Alessio D, Sandoval D, Seeley R. New ways in which GLP-1 can regulate glucose homeostasis. *J Clin Invest.* 2007; 115(12): 3406-3408.
6. Mallette L E, Exton, J H, Park C R. Control of Gluconeogenesis from Amino Acids in the Perfused Rat Liver. *Journal of Biological Chemistry.* 1969; 244(20): 5713-5723.
7. Toft-Nielsen M-B, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab.* 2001; 86(8): 3717-3723.
8. Diao J, Asghar Z, Chan C, Wheeler M. Glucose-Regulated Glucagon Secretion Requires Insulin Receptor Expression in Pancreatic α -Cells. *Journal of Biological Chemistry.* 2005.
9. Nowak T V, Johnson C P, Kalbfleisch J H, Roza A M, Wood C M, Weisbruch J P, Soergel K H. Highly variable gastric emptying in patients with insulin dependent diabetes mellitus. *Gut.* 1995; 37: 23-29.
10. Drucker D. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: Preclinical biology and mechanisms of action. *Diabetes Care.* 2007.
11. Egan J, Clocquet A, Elahi D. The Insulinotropic Effect of Acute Exendin-4 Administered to Humans: Comparison of Nondiabetic State to Type 2 Diabetes. *J Clin Endocrinol Metab.* 2002; 3: 1282-1290.
12. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes. *Vasc Health Risk Manag.* 2008; 4(4): 753-768.
13. Medline Plus Medical Dictionary. Available at: <http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=agonist>. Accessed November 24, 2009.
14. Lamot B, Drucker D. Differential Antidiabetic Efficacy of Incretin Agonists Versus DPP-4 Inhibition in High Fat–Fed Mice. *Diabetes.* 2007; 57: 190-198.
15. Nathan D, Buse J, Davidson M, Ferrannini E, Holman K, Sherwin R, Zinman B. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care.* 2008; 31(12): 1-11.
16. 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.

17. DeFronzo R, Ratner R, Han J, Kim D, Fineman M, Baron A. Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes. *Diabetes Care*. 2005; 28(5):1092-1100.
18. Fehse F, Trautmann M, Holst JJ, Halseth A, Nanayakkara N, Nielsen L, Fineman M, Kim D, Nauck M. Exenatide Augments First- and Second-Phase Insulin Secretion in Response to Intravenous Glucose in Subjects with Type 2 Diabetes. *J Clin Endocrinol Metab*. 2005; 90(11): 5991–5997.
19. IMS Heath data, October 2009.
20. SDI data, March 2009.

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