

Gvoke HypoPen: An Auto-Injector Containing an Innovative, Liquid-Stable Glucagon Formulation for Use in Severe Acute Hypoglycemia

Damianne Brand-Eubanks

Introduction

The use of insulin to decrease complications associated with diabetes currently focuses on attempts to control elevated glucose levels. This has often been balanced with a calculated risk potential for over-treatment and resultant hypoglycemia. This subsequent hypoglycemia can have a greater effect on morbidity and mortality for patients with type 1 diabetes, who are reliant on exogenous insulin, and extreme hypoglycemic events are directly associated with substantial overall health care costs (1). Current therapy for acute, severe hypoglycemia includes a glucagon emergency kit (GEK), which is effective when used correctly. However, training on how to appropriately assemble the GEK is rare, and administration of emergency glucagon can be complicated for the inexperienced.

Glucagon, a peptide hormone normally produced endogenously in the pancreas, acts as an agonist at the glucagon receptor, initiating a pathway resulting in the conversion of glycogen in the liver to the more accessible form of glucose that can be released into the blood. Exogenous glucagon is currently available in a powder that must be reconstituted in solution immediately before intramuscular or intravenous delivery due to its instability in solution (2,3). Xeris Pharmaceuticals has submitted new drug applications to both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for a new glucagon

formulation addressing the historical complication of instability in solution. The company proposes a novel, ready-to-use, liquid-stable glucagon in an auto-injector that does not require mixing before use.

Indications

On its new drug application (NDA), the manufacturer is seeking an indication for the treatment of severe acute hypoglycemia in patients with diabetes treated with insulin. The company is also seeking an orphan drug status designation with indications for congenital hyperinsulinemic hypoglycemia and post-bariatric surgery hypoglycemia.

Mechanism of Action

The Gvoke HypoPen subcutaneously administers a liquid-stable but nonaqueous glucagon formulation that contains a human recombinant DNA-derived amino acid polypeptide similar to that used in the currently available GEK. Glucagon is an agonist for glycogen receptors, initiating the conversion of stored glycogen into glucose and thereby increasing the concentration of glucose in the blood.

The glucagon formulation is packaged in a ready-to-deliver auto-injector similar to the epinephrine rescue pens used for anaphylaxis. A freeze-dried powder that contains glucagon; trehalose, hydroxyethyl, or a similar starch with a glycine buffer (maintaining a pH of 2.0–3.5); a surfactant; an antioxidant; and a chelating agent is combined with a polar aprotic liquid comprising triacetin, thereby prevent-

Department of Pharmacotherapy, Yakima Extension, Washington State University College of Pharmacy and Pharmaceutical Sciences, Yakima, WA

Corresponding author: Damianne Brand-Eubanks, dbrand@wsu.edu

<https://doi.org/10.2337/cd19-0040>

©2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See www.diabetesjournals.org/contentlicense for details.

ing the aggregation and fibrillation of the glucagon that is normally propagated by aqueous solutions. This process creates a low-volume, highly concentrated solution (4). The auto-injector will be available in two premeasured doses: a 0.5 mg/0.1 mL dose for pediatric administration and a 1 mg/0.2 mL dose for adolescent and adult administration (5).

Potential Advantages

The ease of use of an auto-injector and a decrease in the number of steps currently required to reconstitute glucagon powder for injection are meaningful advantages. The auto-injector was shown to have a significantly higher success rate in delivering a full glucagon dose during simulated emergencies with both trained and untrained users (6). The glucagon auto-injector also more quickly resolved global hypoglycemia symptoms compared to the current GEK (6).

This novel delivery system requires only two simple steps. First, users must remove the cap from the pen. Second, they must press the auto-injector against the skin, holding for 5 seconds. Upon contact with the skin, the auto-injector delivers a rescue dose of glucagon (6). No calibration of the dose is required (6).

Additionally, with this device, there is no exposed needle. The needle is protected by a sheath guard, and the needle itself retracts into the body of the auto-injector after administration, making unintentional needle sticks less likely. Due to the low volume of the dose, there is less associated injection-site pain than compared to the GEK (4). Finally, studies indicate that the

medication in this device can be stored at room temperature for 2 years with no refrigeration required at any time (4).

Potential Disadvantages

This nonaqueous solution is delivered subcutaneously, so it does not decrease the potential side effects of nausea and vomiting associated with parenterally delivered glucagon compared to the GEK (6).

Cost

A link between more prompt treatment and length of hospital stay has been established through historical data associated with the GEK, and ease of use may lead to a decrease in overall health care costs (7). However, because this novel glucagon product has not yet been approved by the FDA, there is currently only speculation regarding its potential market price. The manufacturer has stated it intends initially to match the current average wholesale price of the GEK auto-injector (5).

Comments

The novel solution technology employed for this product may have implications for use with future glucagon delivery designs such as a bihormonal artificial pancreas closed-loop system that delivers both insulin and glucagon (5). An additional liquid-stable glucagon analog formulation in development by Adocia may create future competition for the Xeris product, leading to subsequent lower costs to consumers.

Bottom Line

This shelf-stable, premixed auto-injector for the treatment of acute hy-

poglycemia has proven to be quicker and less complicated to administer by trained and untrained users alike, with a 99% success rate for full dose delivery (6). The Gvoke HypoPen auto-injector is equally efficacious compared to the currently available GEK for use in adults and children (5).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Cryer PE, Davis SN, Shamooh H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–1912
2. Kedia N. Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. *Diabetes Metab Syndr Obes* 2011;4:337–346
3. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 2018;46:D1074–D1082
4. Newswanger B, Ammons S, Phadnis N, et al. Development of a highly stable, nonaqueous glucagon formulation for delivery via infusion pump systems. *J Diabetes Sci Technol* 2015;9:24–33
5. Xeris Pharmaceuticals, Inc. Annual report pursuant to section 13 or 15 of the Securities Exchange Act of 1934. 6 March 2019. Available from www.xerispharma.com/images/xeris-annual-report-2018.pdf. Accessed 20 May 2019
6. Christiansen M, Cummins M, Prestrelski S, Junaidi K. A phase 3 comparison of a ready-to-use liquid glucagon rescue pen to glucagon emergency kit for the symptomatic relief of severe hypoglycemia. Poster presented at the Diabetes Technology Society's Diabetes Technology Meeting, 8–10 November 2018, Bethesda, Md.
7. Bajpai S, Poehlmann J, Osumili B, Mitchell B, Valentine W. Nasal glucagon saves professional emergency medical (EM) costs versus intramuscular glucagon: a US based cost-offset model. *Value Health* 2018;21(Suppl. 1):S76