**Medicare/Medicaid State Testimony**

- The American Diabetes Association (ADA) defines severe hypoglycemia (Level III) as a condition where a person with diabetes (PWD) experiences very low blood sugar level with severe cognitive impairment, that requires external assistance in order to recover.[1]
    - If left untreated, severe hypoglycemia may worsen to coma, seizure, or death. A first line therapy for severe hypoglycemia is the administration of glucagon, a drug that raises blood sugar.[1]
    - Glucagon is recommended when a PWD who experiences any hypoglycemia is unwilling or unable to consume oral carbohydrates.[1,2] The ADA Standards of Medical Care state that glucagon should be prescribed for all individuals who are at increased risk of experiencing a low blood glucose < 54 mg/dL (Level II).
- Over 30 million children and adults in the United States have diabetes.[3]
    - Approximately 5% of the population with diagnosed diabetes have type 1 diabetes (T1D) and approximately 90-95% has type 2 diabetes (T2D).
    - 83% of all PWDs take medications that include oral and/or injectable antihypoglycemic drugs.
- The use of insulin by itself or in combination with other drugs can significantly increase the risk of hypoglycemia - which left untreated may lead to severe hypoglycemia.
    - Approximately 7.4 million PWDs in the United States use insulin. In 2014, there were 14.2 million emergency department (ED) visits for adults aged 18 years or older with hypoglycemia as the first-listed diagnosis and diabetes as another diagnosis; 245,000 of these ED visits (11.2 per 1,000 PWDs) are for severe hypoglycemia.
    - Approximately 25% of patients who visit the ER for severe hypoglycemia are hospitalized.
- While glucagon is widely recommended as a readily available rescue therapy, less than 10% of PWDs in the United States are in possession of glucagon during an emergency as reported in one survey study of 264 participants with T1D.[4]
    - Reasons behind this may include the poor usability of marketed powder glucagon.
    - Currently available lyophilized glucagon emergency kits have a multi-step preparation/administration process that is both cumbersome and difficult.[5,6]
    - In a real-world study, 69% of parents describe multiple handling difficulties with powder glucagon and share concerns about their ability to successfully prepare and administer a full dose of glucagon during emergency settings.[7]
- On September 10, 2019, FDA approved the first and only premixed, prefilled, premeasured, liquid stable glucagon, GVoke™ PFS (glucagon injection) Pre-filled Syringe and Gvoke Hypopen™ (glucagon injection) which are antihypoglycemic agents indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.[8]
    - Both dosage forms are ready-to-use preparations with a 2-step administration process that should be stored at room temperature and have a 24-month shelf life.[8]
- Since Xeris followed the 505(b)(2) regulatory pathway for Gvoke NDA, it was necessary to compare efficacy and safety variables against that of the Reference Listed Drug, Eli Lilly Glucagon 1mg (GEK).[9]
- Gvoke was evaluated in adult patients aged 18 to 74 years with type 1 diabetes in two multi-center, non-inferiority, blinded, randomized, controlled, crossover studies: Study A with 80 patients, and 81 patients in Study B.[8]
    - The efficacy of Gvoke was compared to GEK in subjects who were in a state of insulin-induced severe hypoglycemia with a confirmed blood glucose < 50 mg/dL.[8]



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    - The primary efficacy endpoint was a plasma glucose level of >70 mg/dL or ≥ 20 mg/dl increase by 30 minutes post-injection, also defined as Treatment Success.
    - Gvoke met the pre-specified non-inferiority margin on both per protocol and intent-to-treat populations.
    - In a pooled analysis, 98.7% in the Gvoke group achieved treatment success with a mean time to treatment success of 13.8 minutes.
- Gvoke was evaluated in 31 pediatric patients with T1D.
    - Patients were administered insulin to induce a low normal glycemic state of < 80 mg/dL and then received an age appropriate dose of Gvoke.[8]
    - Patients ages 2 to < 12 years of age received a 0.5 mg dose of Gvoke, and patients ages 12 to < 18 years of age also received a 1 mg dose of Gvoke.
    - All evaluable pediatric patients (30/30) achieved a target glucose increase of at least 25 mg/dL, 30 minutes after receiving Gvoke.
    - Following administration of glucagon, plasma glucose levels over time showed a similar rise in blood glucose across each pediatric age group.
- Most common adverse reactions (incidence ≥ 2%) reported were nausea, vomiting, headache, and injection site edema raised ≥1 mm for adults and nausea, vomiting, hypoglycemia, headache, hyperglycemia, injection site reaction and discomfort, urticaria, and abdominal pain for pediatrics.[8]
- Contraindications include: pheochromocytoma, insulinoma and a known hypersensitivity to glucagon or to any of the excipient.
- Warnings and Precautions include catecholamine release in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, lack of efficacy in patients with decreased hepatic glycogen, necrolytic migratory erythema, hypoglycemia in patients with glucagonoma.
- Functional efficacy (the ability to deliver a full dose of drug) and usability were evaluated in two human factor studies using the Gvoke PFS in a simulated severe hypoglycemia rescue situation.[10]
    - Participants included adult and adolescent, experienced and naïve caretakers, as well as First Responders.
    - A formative study demonstrated that all 11 study participants could successfully administer a full dose of glucagon dose using a prefilled syringe.
    - A subsequent summative validation study demonstrated that all 75 study participants were able to successfully deliver the rescue injection using the Gvoke PFS without directed guidance.
    - The summative study demonstrated that within a simulated emergency setting 99% of study participants, on their first attempt, delivered the full dose of glucagon.

Gvoke is available as:

- 0.5 mg/0.1 mL single-dose pre-filled syringe
- 1 mg/0.2 mL single-dose pre-filled syringe

In 2020, the Hypopen Autoinjector will be available as:

- 0.5 mg/0.1 mL single-dose pre-filled HypoPen auto-injector
- 1 mg/0.2 mL single-dose pre-filled HypoPen auto-injector

**References**

1. ADA Standards of Medical Care. Diabetes Care 2019;42(Suppl. 1): S61–S70. 2. International Hypoglycemia Study Group. Diabetes Care 2017; 40:155–157. 3. ADA FAST FACTS. Data and Statistics about Diabetes. https://professional.diabetes.org/content/fast-facts-data-and-statistics-about-diabetes; Accessed July 29, 2019. 4. Haymond MW, Liu J, Bispham J, Hickey A, McAuliffe-Fogarty AH. Clin Diabetes. 2019 Apr;37(2):162-166. 5. Glucagon™ (glucagon for injection) [Information for the User] Indianapolis, IN: Lilly USA; 2018. 6. GlucaGen® Hypokit® (glucagon) [Instructions for Use] Plainsboro, NJ; 2018. 7. Kedia N. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2011:4 337–346. 8. Gvoke™ [prescribing information]. Chicago, IL: Xeris Pharmaceuticals, Inc. 2019. 9. Data on file. Xeris Pharmaceuticals, Inc. 10. Newswanger B, Prestrelski S, Andre AD. Human factors studies of a prefilled syringe with stable liquid glucagon in a simulated severe hypoglycemia rescue situation. Expert Opin Drug Deliv. 2019;16(9):1015-1025.