# Therapeutic Class Overview
## Glucagon agents

## INTRODUCTION

- Hypoglycemia in patients with diabetes can be defined as episodes of abnormally low plasma glucose concentration that expose the individual to potential harm. An alert value for hypoglycemia is defined as blood glucose < 70 mg/dL. Clinically important hypoglycemia is defined as blood glucose < 54 mg/dL, but the physiologic response to low blood glucose can be variable (*American Diabetes Association [ADA] 2020*, *Cryer 2019*).
- Hypoglycemia frequently affects patients with type 1 diabetes (T1DM), in whom the risk of severe hypoglycemia (episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) increases with intensive therapy. Patients with T1DM report an average of up to 3 episodes of severe hypoglycemia per year. Severe hypoglycemia affects patients with type 2 diabetes (T2DM) less commonly; those who are treated with a sulfonylurea, a meglitinide, or insulin are generally at higher risk (*Cryer 2019, Seaquist et al 2013*).
  - In 2014, the Centers for Disease Control and Prevention (CDC) reported 245,000 episodes of hypoglycemia resulted in emergency department visits (incidence ratio of 11.2 per 1000 patients with diabetes).
- Hypoglycemia causes symptoms such as tremor, anxiety, tachycardia, sweating, hunger, dizziness, weakness, drowsiness, confusion, and possibly, seizure and coma at lower plasma glucose concentrations. Although extreme, prolonged hypoglycemia can cause brain death, the majority of episodes are reversed after the glucose level is raised. Rare fatal episodes are generally thought to be due to other mechanisms such as ventricular arrhythmia (*Cryer 2019, Seaquist et al 2013*).
- The goal of treatment of hypoglycemia is to normalize the plasma glucose concentration by administering carbohydrates (dietary or parenteral according to the level of consciousness), or in cases of severe hypoglycemia, by administering glucagon (*Cryer 2019*).
  - Patients with symptomatic hypoglycemia should ingest glucose in the form of tablets, juice, milk, other snacks, or a meal.
  - Patients with severe hypoglycemia can usually be treated quickly by giving intravenous (IV) dextrose.
  - In a person with impaired consciousness and no established IV access, administration of glucagon (subcutaneously [SC], intramuscularly [IM], or intranasally [IN]) by a second party will usually lead to recovery of consciousness within approximately 15 minutes, although it may be followed by marked nausea or even vomiting.
    - The response to IV glucose and glucagon is transient; therefore, treatment of hypoglycemia often needs to be followed by a continuous infusion of glucose or by intake of food if the patient is able to eat.
- Injectable glucagon has been approved for use in the U.S. for several decades (*Baqsimi FDA News Release 2019*). A few injectable products (ie, GlucaGen and Glucagon Emergency Kits [GEKs] by Lilly [GEK-L] and Fresenius Kabi [GEK-F]) have been approved for SC or IM administration that require the caregiver to reconstitute the glucagon powder with the diluent prior to injection. A recently approved product, Gvoke (glucagon injection), is available as an auto-injector or prefilled syringe for SC administration and does not require reconstitution. Baqsimi (glucagon nasal powder) is the first IN administered glucagon to be approved; it can be delivered by placing the tip of the device in one nostril and depressing a small plunger that discharges the powder into the nostril without need for inhalation from the patient (*Cryer 2019*).
- Medispan Class: Glucagon

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| Baqsimi (glucagon) | - |
| GlucaGen HypoKit (glucagon) | - |
| Glucagon Emergency Kit (glucagon)* | - |
| Gvoke (glucagon)† | - |

* Products from Lilly and Fresenius Kabi

†The prefilled syringe formulation is currently available; the auto-injector formulation will be launched at a later date.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | Baqsimi (glucagon) | GEK-F/GEK-L | GlucaGen HypoKit (glucagon) | Gvoke (glucagon) |
|---|---|---|---|---|
| Severe hypoglycemia in patients with diabetes | ✔ (≥ 4 years of age) | ✔ (all ages) | ✔ (all ages) | ✔ (≥ 2 years of age) |

Note: GlucaGen and the GEKs are indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. This indication is not addressed in this review

(*Prescribing information: Baqsimi 2019, GlucaGen HypoKit 2018, GEK-F 2019, GEK-L 2019, Gvoke 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Two randomized, open-label (OL), 2-period, crossover (XO), noninferiority studies compared the efficacy of a single 3 mg dose of Baqsimi to a single 1 mg dose of IM glucagon injection (GlucaGen) for treatment of insulin-induced hypoglycemia in adults with diabetes. One of the studies included 70 adult patients with T1DM, while the other study included 83 adult patients with T1DM or T2DM. The primary outcome measure was the proportion of patients achieving treatment success, defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon (*Baqsimi prescribing information 2019*, *Data on file [Eli Lilly and Company] 2019*, *Rickels et al 2016*).
  - In both studies, Baqsimi demonstrated noninferiority to IM glucagon in reversing insulin-induced hypoglycemia (98.8 to 100% for Baqsimi vs 100% for IM glucagon). In one study, the mean time to treatment success was 11.6 minutes for the Baqsimi group vs 9.9 minutes for the IM glucagon group while in the other study, the mean time to treatment success was 15.9 minutes for Baqsimi group vs 12.1 minutes for the IM glucagon group.
- In a pediatric study of 48 patients aged ≥ 4 years with T1DM, similar results for Baqsimi 3 mg vs weight-based (0.5 mg or 1 mg) IM glucagon were observed. The primary endpoint was the percentage of patients with a glucose increase of ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon administration (*Baqsimi prescribing information 2019*, *Data on file [Eli Lilly and Company] 2019, Sherr et al 2016*).
  - Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥ 20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase ≥ 20 mg/dL ranged from 10.8 to 14.2 minutes for Baqsimi and 10.8 to 12.5 minutes for IM glucagon.
- In a comparative usability study (N = 31) evaluating the use of Baqsimi and IM glucagon by individuals in a simulated emergency event, participants were significantly more likely to successfully administer a full dose with Baqsimi (94% of attempts) than with injectable glucagon (13% of attempts) (*Yale et al 2017*).
- In 2 OL, real-world usability studies involving caregivers of adults with T1DM (N = 69) and caregivers of children with T1DM (N = 15), Baqsimi was successful in treating episodes of moderate and severe hypoglycemia in 95.7% of adults and 100% of children. Of note, the trials had serious quality limitations and additional data are needed to validate the results (*Deeb et al 2018, Seaquist et al 2018)*.
- Two randomized, 2-way, XO, noninferiority studies (N = 181) compared the efficacy of Gvoke 1 mg SC to GEK-L 1 mg SC for treatment of insulin-induced hypoglycemia in adults with T1DM. The primary efficacy endpoint was the proportion of patients achieving treatment success, defined as either an increase in plasma glucose from a mean value at the time of glucagon administration to an absolute value ≥ 70 mg/dL or a relative increase of ≥ 20 mg/dL at 30 minutes after receiving study glucagon (*Gvoke prescribing information 2019, Christensen et al 2019 [poster]*).
  - In a pooled analysis of both studies, the proportion of patients who achieved treatment success was 99% in the Gvoke group and 100% in the GEK-L group, and the comparison between groups met the prespecified non-inferiority

margin. The mean time to treatment success was 13.8 minutes in the Gvoke group and 10 minutes in the GEK-L group.

- An OL study of 31 patients aged ≥ 2 years with T1DM evaluated 2 doses of Gvoke for treatment of insulin-induced hypoglycemia. Patients aged 2 to < 6 years and 6 to < 12 years received Gvoke 0.5 mg SC while patients aged ≥ 12 years received either Gvoke 0.5 mg or 1 mg SC (*Gvoke prescribing information 2019*, *Buckingham et al 2018 [poster]*).
  - All evaluable patients achieved a target dose of at least 25 mg/dL.
- Two human factors studies evaluated whether the Gvoke prefilled syringe could be effectively administered (*Newswanger et al 2019*). In a formative study (N = 11), there was a 100% success rate while in the validation study (N = 75), 99% of patients successfully administered the full dose. Similarly, 2 human factors studies evaluated whether the Gvoke auto-injector could be effectively administered (*Valentine et al 2019*). In the simulated-use comparative usability study (N = 16), 88% of participants were able to successfully administer a rescue injection using Gvoke compared with 31% with the GEKs. In the validation study (N = 75), 98.7% of patients successfully administered the rescue injection using the Gvoke auto-injector.

## CLINICAL GUIDELINES

- ADA guidelines recommend that all patients at increased risk of hypoglycemia with blood glucose < 54 mg/dL be prescribed glucagon so that it would be available if needed. Caregivers, school personnel, or family members should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals, particularly with the availability of IN and stable soluble glucagon available in auto-injector pens (*ADA 2020*).
- The American Association of Clinical Endocrinologists/American College of Endocrinology guidelines recommend that SC or IM glucagon or IV glucose be given by a trained family member or medical personnel to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*Handelsman et al 2015*).

## SAFETY SUMMARY

- All glucagon products are contraindicated in patients with known hypersensitivity to any of the constituents of the formulation, and they all carry a warning for lack of efficacy in patients with decreased hepatic glycogen. They are also contraindicated or have a warning for patients with pheochromocytoma and insulinoma. The injectable products also have a warning for necrolytic migratory erythema due to postmarketing reports following continuous glucagon infusion.
- The most common adverse events (AEs) with Baqsimi were nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, and itchy nose, throat and eyes. Common AEs with the injectable products included nausea, vomiting, and injection site reactions.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| Baqsimi (glucagon) | Nasal powder | IN | One actuation of the IN device into 1 nostril; if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance | The dose should be administered by inserting the tip into 1 nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled. |
| GEK-F (glucagon) | Injection (kit requiring reconstitution) | IM, IV, SC | One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new kit may be administered | The product should be reconstituted according to instructions before administration. |
| GEK-L (glucagon) | | | | |

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| GlucaGen HypoKit (glucagon) | | | while waiting for emergency assistance | Common SC/IM injection sites are the upper arms, thighs or buttocks. |
| Gvoke (glucagon) | Injection (auto-injector, prefilled syringe) | SC | One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance | The injection may be given in the lower abdomen, outer thigh, or outer upper arm. |

See the current prescribing information for full details

## CONCLUSION

- Severe hypoglycemia is generally defined as a hypoglycemic event that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action. Immediate treatment is necessary to increase blood sugar and prevent serious complications, such as loss of consciousness, seizure, coma, or death.
- Treatment guidelines recommend that glucagon be given by a trained caregiver to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*ADA 2020*, *Handelsman et al 2015).*
- Injectable glucagon in the form of kits containing a prefilled syringe of diluent and a vial of glucagon powder for reconstitution has been approved for use in the U.S. for many years. Two new glucagon formulations have been approved that provide additional options for the treatment of severe hypoglycemia in patients with diabetes that may simplify the process of glucagon administration. Gvoke is available in the form of an auto-injector or prefilled syringe that does not require reconstitution, while Baqsimi is the first IN formulation of glucagon.

## REFERENCES


- American Diabetes Association (ADA). Standards of Medical Care in Diabetes−2020. https://care.diabetesjournals.org/content/diacare/suppl/2019/12/20/43.Supplement_1.DC1/DC_43_S1_2020.pdf. Accessed January 13, 2020.
- Baqsimi [package insert], Indianapolis, IN: Lilly USA, LLC; July 2019.
- Buckingham B, Cummins M, Prestrelski S, Strange P. Liquid room temperature stable glucagon—glucose response in pediatric type 1 diabetes patients. Poster presented at: American Diabetes Association 78th Scientific Sessions; Orlando, Florida, June 22–26, 2018.
- Centers for Disease Control and Prevention. National Diabetes Statistics Report 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed December 16, 2019.
- Christiansen M, Cummins M, Prestrelski S, Junaidi MK. An integrated summary of safety and efficacy of a ready-to-use liquid glucagon rescue pen for the treatment of severe hypoglycemia in adults. Poster presented at American Diabetes Association 79th Scientific Sessions, June 7–11, 2019, San Francisco, CA.
- Cryer PE. Hypoglycemia in adults with diabetes mellitus. www.uptodate.com. Updated September 16, 2019. Accessed December 16, 2019.
- Data on file; Eli Lilly and Company; 2019.
- Deeb LC, Dulude H, Guzman CB, et al. A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycemia in children and adolescents with type 1 diabetes in the home or school setting. *Pediatr Diabetes*. 2018;19(5):1007-1013.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed December 16, 2019.
- FDA News Release: FDA approves first treatment for severe hypoglycemia that can be administered without an injection. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-severe-hypoglycemia-can-be-administered-without-injection. July 24, 2019. Accessed December 16, 2019.
- GlucaGen HypoKit [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; July 2018.
- Glucagon Emergency Kit [package insert], Indianapolis, IN: Lilly USA, LLC; July 2019.
- Glucagon Emergency Kit [package insert], Lake Zurich, IL: Fresenius Kabi; September 2019.
- Gvoke [package insert], Chicago, IL: Xeris Pharmaceuticals Inc., September 2019.
- Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan—2015—Executive Summary. *Endocr Pract*. 2015;21(4):413-37.
- 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.

- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed December 16, 2019.
- Rickels MR, Ruedy KJ, Foster NC, et al.; T1DM Exchange Intranasal Glucagon Investigators. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: A randomized crossover noninferiority study. *Diabetes Care*. 2016;39(2):264-270.
- Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384-1395.
- Seaquist ER, Dulude H, Zhang XM, et al. Prospective study evaluating the use of nasal glucagon for the treatment of moderate to severe hypoglycaemia in adults with type 1 diabetes in a real-world setting. *Diabetes Obes Metab*. 2018;20(5):1316-1320.
- Sherr JL, Ruedy KJ, Foster NC, et al.; T1DM Exchange Intranasal Glucagon Investigators. Glucagon nasal powder: A promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care*. 2016;39(4):555-562.
- Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. *Diabetes Technol Ther*. 2019 ;21(9):522-530.
- Yale JF, Dulude H, Egeth M, et al. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: A simulation study. *Diabetes Technol Ther*. 2017;19(7):423-432.


Publication Date: January 13, 2020