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. According to the American Diabetes Association (ADA), clinically important hypoglycemia is defined as blood glucose < 70 mg/dL. Level 1 hypoglycemia presents as blood glucose readings ranging from 54 to 69 mg/dL, level 2 hypoglycemia as blood glucose < 54 mg/dL, and level 3 hypoglycemia as a severe event marked by altered mental and/or physical functioning. Blood glucose < 54 mg/dL requires immediate action to resolve hypoglycemia (*ADA 2021*, *Cryer 2021*).
- 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 2021*).
  - In 2016, the Centers for Disease Control and Prevention (CDC) reported 235,000 episodes of hypoglycemia resulted in emergency department visits (incidence ratio of 10.2 per 1000 patients with diabetes) (*CDC 2020*).
- 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 2021*).
- 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 2021*).
  - Patients with symptomatic hypoglycemia should ingest glucose in the form of tablets, sweetened fruit juice, or hard candy; glucose tablets have more consistent effectiveness.
  - Patients with severe hypoglycemia can usually be treated quickly by giving intravenous (IV) dextrose or glucagon, depending on the status of IV access.
  - 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 United States (US) for several decades. A few injectable products (eg, GlucaGen and Glucagon Emergency Kits [GEKs] by Eli 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. Gvoke (glucagon injection) is available as an auto-injector or prefilled syringe for SC administration and does not require reconstitution. Baqsimi (glucagon nasal powder) was 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. Zegalogue (dasiglucagon), a glucagon analog, was approved in March 2021; it is available as an auto-injector or prefilled syringe for SC administration that does not require reconstitution (*Cryer 2021*).
- Medispan Class: Antidiabetics; Diabetic Other; Glucagon

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Baqsimi (glucagon)	-
GlucaGen HypoKit (glucagon)	-
Glucagon emergency kit or solution (glucagon)*	✔
Gvoke (glucagon)	-

Drug	Generic Availability
Zegalogue (dasiglucagon)	-

* Products from Eli Lilly and Fresenius Kabi; a generic of the Eli Lilly product is available

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Baqsimi (glucagon)	GEK-F*/GEK-L*	GlucaGen HypoKit* (glucagon)	Gvoke (glucagon)	Zegalogue (dasiglucagon)
Severe hypoglycemia in patients with diabetes	✔ (≥ 4 years of age)	✔ (all ages)	✔ (all ages)	✔ (≥ 2 years of age)	✔ (≥ 6 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 2021, GlucaGen HypoKit 2021, GEK-F 2019, GEK-L 2021, Gvoke 2021, Zegalogue 2021*)

- 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 2021*, *Rickels et al 2016, Suico et al 2020*).
  - 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 2021*, *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)*.
- A study (N = 65) compared the success rates of administering IN glucagon vs injectable glucagon by trained and untrained patients with diabetes. Of all patients (trained and untrained), 90.6% successfully administered IN glucagon and 7.9% successfully administered injectable glucagon (*Settles et al 2020*).

- A meta-analysis (MA) of 8 studies (N = 269) compared the effectiveness of IN glucagon with IM/SC glucagon in patients with T1DM and hypoglycemia. The response outcomes were similar between IN glucagon and IM/SC glucagon (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.28 to 2.32) (*Pontiroli et al 2020*).
- 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 2021, 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 2021*, *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.
- Dasiglucagon was evaluated in 3 Phase 3, double-blind, multi-center, randomized, placebo-controlled trials in patients with T1DM. Two trials were conducted in adult patients (trials A and B) and 1 trial was conducted in pediatric patients aged 6 to 17 years (Trial C). Patients were randomized to dasiglucagon 0.6 mg SC, placebo, or (in Trials A and C only) glucagon 1.0 mg SC (GlucaGen) following a controlled induction of hypoglycemia using IV insulin. The primary efficacy endpoint for all 3 trials was time to plasma glucose recovery (treatment success), defined as an increase in blood glucose of ≥ 20 mg/dL from time of administration, without additional intervention within 45 minutes. The primary hypothesis test was superiority of dasiglucagon vs placebo; there was no formal hypothesis test of dasiglucagon vs glucagon injection *(Battelino et al 2021, Pieber et al 2021, Zegalogue Prescribing Information 2021).*
  - In trial A (N = 170), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 40 minutes, respectively; p < 0.001). The median time to plasma glucose recovery was numerically similar between dasiglucagon and glucagon injection (10 minutes and 12 minutes, respectively).
  - In trial B (N = 45), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 35 minutes, respectively; p < 0.0001).
  - In trial C (N = 42), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 30 minutes, respectively; p < 0.0001). The median time to plasma glucose recovery was numerically similar between dasiglucagon and glucagon injection (10 minutes and 10 minutes, respectively).

CLINICAL GUIDELINES

- ADA guidelines recommend that all patients at increased risk of hypoglycemia with blood glucose < 54 mg/dL or hypoglycemia marked by altered mental and/or physical functioning 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 2021*).
- 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 of the glucagon products have contraindications and/or warnings in patients with pheochromocytoma, insulinoma, and known hypersensitivity to any of the constituents of the formulation. In addition, they all carry a warning for lack of efficacy in patients with decreased hepatic glycogen. Gvoke, GlucaGen, and the GEKs also have a warning for necrolytic migratory erythema (NME) 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) GEK-L (glucagon) GlucaGen HypoKit (glucagon)	Injection (including a 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 while waiting for emergency assistance	The product should be reconstituted according to instructions before administration. 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.
Zegalogue (dasiglucagon)	Injection (auto-injector, prefilled syringe)	SC	One dose (0.6 mg); 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, buttocks, 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 2021*, *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 US for many years. Recently, new products 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 and dasiglucagon (a glucagon analog) are 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.

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