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Drug Class Update with New Drug Evaluation: Glucagon

Date of Review: December 2021

Date of Last Review: February 2020
Dates of Literature Search: 12/01/2019 - 08/06/2021
Brand Name (Manufacturer): Zegalogue (Zealand Pharma)
Dossier Received: no

Generic Name: dasiglucagon

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: The purpose of the glucagon class update is to evaluate new literature published since the last review and to evaluate the efficacy and safety of dasiglucagon, a new glucagon formulation.

Research Questions:
1. What is the new comparative evidence for efficacy of the different glucagon formulations (i.e., intranasal, subcutaneous [SC], intramuscular [IM], intravenous [IV]) used for the treatment of severe hypoglycemia for the outcomes of time to glucose normalization and resolution of hypoglycemia symptoms?
2. What is the comparative evidence for safety between the different glucagon formulations?
3. Are there subpopulations based on specific demographic characteristics in which certain glucagon formulations would be more effective or cause less harm in the treatment of hypoglycemia?

Conclusions:
- There was no new, high quality, comparative evidence identified for the different glucagon formulations.
- Three trials informed the approval of dasiglucagon: 2 trials in adults and one trial in children and adolescents. The overwhelming majority of study participants in the dasiglucagon trials were white (range, 92% to 100%) and the drug was studied in a tightly controlled inpatient setting. These factors reduce the applicability to the Oregon Medicaid population. There is moderate quality evidence that dasiglucagon improves time to plasma glucose recovery relative to placebo.
    - In adult patients, time to glucose recovery was 10 minutes compared to 35-40 minutes for placebo (P<0.001 for both studies; no confidence intervals [CI] provided).[1,2]
    - In children and adolescents (ages 6-17 years) time to glucose recovery was 10 minutes for dasiglucagon and 35 minutes for placebo (P<0.001; no CI provided).[3]

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- Two trials used glucagon as an active control (no formal statistical comparisons). Results of glucose recovery within 30 minutes suggest similar efficacy between dasiglucagon and glucagon.[2,3]

- Adverse events that occurred more often with dasiglucagon compared to placebo were nausea, vomiting, headache and injection site pain. No serious adverse events were reported.[4]
- New contraindications were added to labeling for generic glucagon, GlucaGen®, Gvoke®, and Baqsimi® products in patients with pheochromocytoma, glucagonoma or insulinoma (**Table 2**).
- There was insufficient evidence to determine if certain glucagon formulations would be more effective or associated with less harm in certain subgroups based on any demographic characteristic.

Recommendations:

- Recommend dasiglucagon remain non-preferred with no changes to the preferred drug list (PDL).
- After evaluation of costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- The glucagon class was last reviewed in February of 2020, at which time a new PDL class was created. Preferred product designation was assigned to one intranasal product and 2 SC products (that require reconstitution); Baqsimi®, GlucaGen®, and glucagon emergency kit, respectively.
- Products requiring prior authorization (PA) are subject to the general non-preferred PA criteria.

Background:

Hypoglycemia requiring treatment is most commonly experienced in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes (T2DM) who use antidiabetic therapies to normalize glucose levels.[5] The prevalence of severe hypoglycemia is thought to be as high as 3 episodes a year in patients with T1DM, but infrequent in patients with T2DM.[5] Hypoglycemia is associated with many symptoms, including tremor, palpitations, anxiety, sweating, hunger and, in rare cases, seizures and coma. Case reports suggest that an average of 7% of deaths in patients with T1DM are due to hypoglycemia.[6] Hypoglycemia symptoms can appear at glucose levels of 65 mg/dL or lower; however, some individuals are less sensitive to glucose changes and are asymptomatic at low blood glucose levels.[5]

Hypoglycemia can be defined as severe hypoglycemia (which requires assistance from another person to administer carbohydrate or glucagon), symptomatic hypoglycemia (symptoms with blood glucose less than 70 mg/dL), asymptomatic hypoglycemia (no symptoms but blood glucose less than 70 mg/dL), and pseudohypoglycemia (typical symptoms are present but glucose values are 70 mg/mL or greater).[5,6]

It is recommended to treat hypoglycemia by administering 15-20 grams of fast-acting carbohydrate, such as glucose tablets, hard candy, or sweetened fruit juice.[7,8] Fifteen grams of glucose is required to increase blood glucose levels approximately 37 mg/dL within 20 minutes.[9] Intravenous dextrose may also be administered by a medical professional in medical emergencies. Administration of glucagon is an option in patients with severe hypoglycemia who are not being treated in a medical setting.[5,7] Glucagon stimulates endogenous glucose production to increase blood glucose levels. Glucagon given SC or IM increases blood glucose 54 mg/dL to 216 mg/dL in 60 minutes.[9] Guidelines recommend patients with T1DM always carry a form of glucagon (subcutaneous, intramuscular or nasal) that can be administered by a caregiver if needed.[10]

Glucagon formulations available in the U.S. include glucagon kits that require reconstitution for injection (e.g., GlucaGen® Hypokit and Glucagon for Injection), ready-to-use SC glucagon injectable products (e.g., Gvoke®) and intranasal glucagon (e.g., Baqsimi®) **(Table 1)**. [11–14] Reconstituted glucagon products can be given SC, IM or IV but the ready-to-use formulations can be administered SC only. Nasal glucagon is administered intranasally via a device which dispenses a glucagon powder that is readily absorbed by the mucous membranes.[5] Administration of IV, IM or SC glucagon is usually associated with glucose recovery in about 15 minutes, while it is slightly longer (about 18 minutes) for intranasally administered glucagon.

Table 1. Approved Glucagon Products

Brand Name (Manufacturer)	Indication(s)	Reconstitution	Strength/Route	Dose and Frequency
Baqsimi®[12] (Lilly)	Treatment of severe hypoglycemia in patients with diabetes ages 4 years and older	No	3 mg intranasal spray powder	1 spray into 1 nostril Dose may repeat once after 15 minutes if no response
GlucaGen®[13] (Novo Nordisk)	Treatment of hypoglycemia; also used as a diagnostic aid	Yes	1 mg/ 1mL SC, IM, IV	Adults and children ≥ 55 lbs. (25 kg) 1 mL Children < 55 lbs. (25 kg): 0.5 mL If weight unknown: Children < 6 years: 0.5 mL Children 6 years and older: 1 mL (must be reconstituted) Dose may be repeated if no response*
Glucagon Emergency kit[11] (Lilly)	Treatment for severe hypoglycemia in patients with diabetes mellitus; also used as a diagnostic aid	Yes	1 mg/ 1 mL SC, IM, IV	Adults and children ≥44 lbs. (20 kg): 1 mg Children <44 lbs. (20 kg): 0.5 mg (or dose equivalent to 20-30 mcg/kg) (1 mg/mL reconstituted) Dose may be repeated if no response*
Gvoke®[14] (Xeris) Pre-filled syringe and auto-injector	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and older	No	0.5 mg/0.1 mL or 1 mg/0.2 mL SC	Adults and pediatric patients 12 years and older: 1 mg Pediatric patients 2 to under 12 years: < 45 kg: 0.5 mg ≥ 45 kg: 1 mg Dose may be repeated after 15 minutes if no response
Zegalogue®[4] (Zealand)	Treatment of severe hypoglycemia in adults and pediatric patients 6 years and older	No	0.6 mg/ 0.6 mL SC	Adults and pediatrics: 0.6 mg Dose may be repeated after 15 minutes if no response

Abbreviations: IM – intramuscular; IV -intravenous; SC – subcutaneous
Key: * Dosing interval not specified

Study endpoints frequently used to determine the efficacy of glucagon products are normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms.

There were 21 claims for glucagon products for Oregon Health Plan (OHP) fee-for-service (FFS) patients last quarter. Most prescription claims were for glucagon kits; however, intranasal glucagon and pre-filled syringes/auto-injectors were also prescribed. GlucaGen®, glucagon emergency kit, and Baqsimi® nasal spray are preferred. All claims were for preferred products. Non-preferred products are subject to the general non-preferred drug PA criteria.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
None were identified.

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[15–17]

New Guidelines:
None identified

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Glucagon	Gvoke Hypopen	July 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with insulinoma because of the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis

Glucagon	NA	July 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure and in patients with glucagonoma when used as a diagnostic aid due to the risk of hypoglycemia
Glucagon	GlucaGen	March 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with glucagonoma when used as a diagnostic aid due to the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis
Glucagon	Baqsimi	October 2020	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with insulinoma because of the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis

Randomized Controlled Trials:
A total of 193 citations were manually reviewed from the initial literature search. After further review, 190 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the evidence table for dasiglucagon (**Table 6**). Full abstracts are included in **Appendix 2**.

NEW DRUG EVALUATION:
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Dasiglucagon works as an antihypoglycemic agent approved for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years or older.[4] Dasiglucagon is available as a ready-to-use product via a prefilled syringe or autoinjector. No reconstitution is required, and dasiglucagon can be stored at room temperature for up to 12 months.[4] Dasiglucagon is a glucagon receptor agonist, which relies on hepatic glycogen to produce the antihypoglycemic effect. Dasiglucagon increases blood glucose concentrations activating hepatic glucagon receptors. This activation results in glycogen breakdown and glucose release from the liver.[4]

Three clinical trials were used for approval of dasiglucagon and are described and evaluated below in **Table 6**. Two trials were conducted in adult patients and had similar trial methodology.[1,2] In the Bailey, et al. trial 44 patients were included in the analysis.[1] The mean age was 41 years, 57% male and 85% white.[1] The mean duration of diabetes was 22.2 years and the mean hemoglobin A1C (A1C) was 7.2%. In the second adult trial (n=170), 92% patients were white with a mean age of 39.1 years and a mean A1C of 7.4%.[2] Baseline characteristics were similar between groups. In both trials, patients were admitted the night before evaluation and fasted the night (starting at 10 pm) before dosing. Insulin was discontinued in advance based on pharmacokinetic profiles (6 to 48 hours). Hypoglycemia was initiated via an IV infusion of glulisine, set to achieve a controlled decline in plasma glucose, with a target plasma glucose level of 55 mg/dL.

Glucose levels were monitored bedside every 10 minutes while glucose was above 110 mg/dL and every 5 minutes when glucose levels were at or below 110 mg/dL. Insulin was stopped when glucoses were reduced to 60 mg/dL or less. Glucose levels were measured 5 minutes after insulin was stopped along with baseline laboratory samples for plasma glucose, dasiglucagon and insulin concentrations.[1,2] No more than 2 minutes later, either dasiglucagon or placebo was administered, as long as glucoses fell between 45-60 mg/dL. Glucagon was used as an active control in two trials (1 adult and 1 pediatric).[2,3] Each patient received one dose of dasiglucagon, placebo or glucagon (active control in two trials, no formal statistical comparison). Products were administered SC in the deltoid or buttocks via an autoinjector by trial personnel. Samples were taken at 2 minutes or less before product administration and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 45, 50, 60, 75 and 90 minutes. Safety assessments were pre-dose and at predefined intervals up to 120 and 300 minutes after dose. A safety follow-up was performed 28 days after dosing. The primary endpoint for both trials was the time to plasma glucose recovery, defined as first increase in plasma glucose of 20 mg/dL or higher from baseline without rescue IV glucose.[1,2]

The third trial involved children and adolescents (n=42) who were predominately white with a mean A1C of 7.6% and average age of 13.1 years. The trial allowed for patients as young as 6 years; however, the youngest participant was 7 years. The FDA allowed for data to be extrapolated for approval down to 6 years.[18] Trial methodology was similar to the adult studies with a few exceptions. One dose of dasiglucagon, placebo or glucagon (active control) were given when indicated. The decline in plasma glucose was stopped at 80 mg/dL, higher than adult trials to ensure safety.[3] The study drug was given if the plasma glucose was between 54 mg/dL and less than 80 mg/dL at 5 minutes. If plasma glucose fell outside this range, then insulin or glucose was given to obtain the appropriate glucose concentration.[3] Samples were taken at 2 minutes or less before product administration and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes. A sample was taken at 60 minutes if the patient was 21 kgs or more. Safety follow up was done at screening, dosing visit and follow-up, 28 days after dose.[3]

For the primary endpoint in the adult trials, dasiglucagon raised plasma glucoses to the recovery point in 10 minutes compared to 35-40 minutes for placebo ($p<0.001$).[1,2] Adults treated with glucagon obtained plasma glucose recovery in 12 minutes, with no formal comparison to dasiglucagon.[2] The number of patients who recovered within 15 minutes was higher with dasiglucagon compared to placebo (absolute risk reduction (ARR) 88%-97%/number needed to treat [NNT] 1-2). One patient in the dasiglucagon group required rescue treatment in one trial.[1] Injection site (e.g., abdomen, buttock or thigh) did not influence time to recovery. In children and adolescents, the primary endpoint of glucose recovery for dasiglucagon was 10 minutes, compared to 30 minutes for placebo and 10 minutes for glucagon.[3] Glucose recovery at 15 minutes was higher with dasiglucagon compared to placebo with and ARR of 95% and NNT of 2.[3]

Evidence suggests that dasiglucagon provides clinically relevant increases in plasma glucose and is an effective treatment option for patients with hypoglycemia. No formal analyses compared dasiglucagon to other antihypoglycemic therapies; however, informal comparisons suggest dasiglucagon has similar efficacy to glucagon. There is insufficient data on time to glucose normalization based on delivery system (ready-to-use versus reconstitution). Limitations to trial findings include a small number of patients enrolled, administration by a professional in an inpatient setting, artificial hypoglycemia induction, the evaluation of only one dose of treatment, insufficient evidence in patients 65 years and older and extensive exclusion criteria. The exclusion of patients with concomitant illnesses, which was not defined, also limits applicability to diabetic patients that often have comorbidities. Differences in the number of males in some of the treatment groups was determined by the FDA to be due to the small sample size and was found to have no treatment interaction.[18]

Clinical Safety:

The most commonly reported adverse events in trials were nausea, vomiting and headache.[4] No serious safety concerns were reported. The development of treatment-emergent anti-drug antibodies occurred in less than 1% of dasiglucagon treated patients. Dasiglucagon should not be taken with warfarin, indomethacin or beta-blockers.

Table 3. Dasiglucagon Adverse Reactions Occurring in ≥2% More Frequently than with Placebo in Adults[4]

Adverse Reaction	Placebo (n=53)	Dasiglucagon (n=116)
Nausea	4%	57%
Vomiting	2%	25%
Headache	4%	11%
Diarrhea	0%	5%
Injection site pain	0%	2%

Table 4. Dasiglucagon Adverse Reactions Occurring in ≥2% More Frequently than with Placebo in Pediatric Patients[4]

Adverse Reaction	Placebo (n=11)	Dasiglucagon (n=20)
Nausea	0%	65%
Vomiting	0%	50%
Headache	0%	10%
Injection site pain	0%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Normalization of glucose to 70 mg/dL or more
2) Resolution of hypoglycemia symptoms
3) Mortality
4) Serious adverse events

Primary Study Endpoint:

1) Time to plasma glucose recovery

Table 5. Pharmacology and Pharmacokinetic Properties[4]

Parameter	
Mechanism of Action	Dasiglucagon is an agonist at the glucagon receptor which stimulates hepatic glucagon receptors causing an increase in blood glucose concentrations, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.
Distribution and Protein Binding	Distribution is 47 L to 57 L after subcutaneous injection Protein binding not described
Elimination	Not described
Half-Life	Approximately 30 minutes
Metabolism	Proteolytic degradation pathways in the blood, liver, and kidney

Abbreviations: L = liters

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints‡	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Bailey, et al. [1] DB, MC, PC, PG, RCT, Phase 3	1. Dasiglucagon 0.6 mg autoinjector 2. Placebo * Each patient only received one dose of medication or placebo	Demographics: Male: - dasiglucagon 47.1%; - Placebo 90% White: - dasiglucagon 100%; - placebo 70% Mean Age: - dasiglucagon 42.2 years; - placebo 36.5 years HbA1c: - dasiglucagon 7.23%; - placebo 7.18% Plasma glucose: - dasiglucagon 55.1 mg/dL; - placebo 54.6 mg/dL Key Inclusion Criteria: - T1DM ≥1 year - Age 18 to 75 years - Insulin use ≥1 year - HbA1c <10% Key Exclusion Criteria: - Clinically significant concomitant illnesses (not described) - Medical histories that could increase early trial withdrawal or potentially confound safety assessment	ITT: 1. 34 2. 10 Attrition: None	Primary Endpoint: Median time to plasma glucose recovery*: 1. 10.0 minutes 2. 35.0 minutes P < 0.001 (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 30 (88%) 2. 0 P<0.01 (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 33 (97%) 2. 5 (50%) P<0.01 (95% CI NR)	NA ARR 88% /NNT 2 ARR 47% /NNT 3	Nausea: 1. 21 (62%) 2. 1 (10%) Vomiting: 1. 10 (29%) 2. 0 (0%) Headache: 1. 4 (12%) 2. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Patients were randomized 3:1 via interactive web response system. Baseline characteristics were not well matched with may introduce bias. Allocation concealment was maintained by both products being administered via identical autoinjectors. Performance Bias: Unclear. Blinding was maintained via treatment assignments only accessible by authorized personnel. Dasiglucagon and placebo were aqueous formulations in identical autoinjectors. Detection Bias: Unclear. Outcome assessment was not described. Statistical analysis was very limited. Attrition Bias: Low. There was no attrition in either group. Analysis was performed on ITT population. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Severely limited external validity to non-white patients. Forced hypoglycemia with controlled administration was performed in a tightly controlled inpatient setting which does not represent real world scenarios. Intervention: Dasiglucagon 0.6 mg was an appropriate dose as determined by phase 2 studies. Comparator: Placebo comparison was appropriate to determine efficacy but comparison with another glucagon treatment would have provided comparative data. Outcomes: Endpoints were appropriate to determine glucose recovery. Setting: Three inpatient treatment centers in the United States

2. Pieber, et al.[2] DB, MC, PC, PG, RCT, Phase 3	1. Dasiglucagon 0.6 mg autoinjector 2. Placebo 3. Glucagon 1 mg (reconstituted)† * Each patient only received one dose of medication or placebo	Demographics: Male: 63% White: 92% Mean Age: 37 years Mean HbA1c: 7.4% Mean Plasma glucose: 58.7 mg/dL Key Inclusion Criteria: - Same as above Key Exclusion Criteria: - Hypoglycemia with seizure in preceding year - Severe hypoglycemia during previous month - Use of beta-blockers, warfarin, indomethacin or anticholinergics drugs daily during previous 28 days	ITT: 1. 82 2. 43 3. 43 Attrition: None	Primary Endpoint: Time to plasma glucose recovery*: 1. 10.0 minutes 2. 40.0 minutes 3. 12 minutes P<0.001 (relative to placebo) (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 81 (99%) 2. 1 (2%) 3. 41 (95%) P<0.001 (relative to placebo) (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 82 (100%) 2. 20 (47%) 3. 43 (100%) P<0.001 (relative to placebo) (95% CI NR)	NA ARR 97% /NNT 1 ARR 53% / NNT 2	Nausea: 1. 45 (55%) 2. 1 (2%) 3. 23 (53%) Vomiting: 1. 19 (23%) 2. 1 (2%) 3. 9 (21%) Headache: 1. 8 (10%) 2. 1 (2%) 3. 4 (9%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 2:1:1 via an interactive web response system. Baseline characteristics were well matched. Performance Bias: High. Medications were different in appearance. Administration was provided by unblinded trial personnel who were not involved in other trial activities. Detection Bias: Unclear. No details on outcome assessment were provided. Limited statistics provided. Attrition Bias: Low. No missing data. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Results are most applicable to younger, white adults. Intervention: Dasiglucagon was an appropriate dose. Comparator: Comparative analysis between dasiglucagon and glucagon would provide data for place in therapy. Outcomes: Outcomes were appropriate to determine glucose recovery. Setting: Germany (2), Austria (1), United States (1) and Canada (1)

3. Battelino, et al. [3] DB, MC, PC, PG, RCT, Phase 3	1. Dasiglucagon 0.6 mg 2. Placebo 3. GlucaGen† * Each patient only received one dose of medication or placebo	Demographics: Male: 32% White: 93% Mean Age: - dasiglucagon 12.5 years; - placebo 15.0 years; - GlucaGen 12.0 years HbA1c: 7.6% Plasma glucose: 72.64 mg/dL Key Inclusion Criteria: - Age 6-17 years - T1DM for ≥1 year - Receiving daily insulin - Body weight ≥20 kg Key Exclusion Criteria: -Insulinoma or pheochromocytoma - Hypoglycemia with seizures or hypoglycemia unawareness (as assessed at the investigator's discretion) in the prior year - Severe hypoglycemia in prior month - Use of beta-blockers, warfarin, indomethacin, anticholinergics or medication known to prolong the QT interval during previous 28 days prior to screening	FAS: 1. 20 2. 11 3. 10 PP: 1. 19 2. 10 3. 9 Attrition: 1. 1 (5%) 2. 1 (9%) 3. 1 (10%)	Primary Endpoint: Time to plasma glucose recovery*: 1. 10 minutes 2. 30 minutes 3. 10 minutes P<0.001 (relative to placebo) (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 19 (95%) 2. 0 (0%) 3. 10 (100%) P<0.001 (relative to placebo) (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 20 (100%) 2. 6 (55%) 3. 10 (100%) P=0.007 (relative to placebo) (95% CI NR)	NA ARR 95% / NNT 2 ARR 45% / NNT 3	Nausea: 1. 13 (65%) 2. 0 (0%) 3. 3 (30%) Vomiting: 1. 10 (50%) 2. 0 (0%) 3. 1 (10%) Headache: 1. 2 (10%) 2. 1 (9.1%) 3. 1 (10%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 2:1:1 via a central, dynamic variance minimization randomization method via an interactive web response system. Baseline characteristics were well matched with the exception of a higher average age in the placebo group compared to the other treatment groups. Performance Bias: High. Medications were different in appearance. Administration was provided by unblinded trial personnel who were not involved in other trial activities. Detection Bias: Unclear. No details on outcome assessment were provided. Statistical analysis was very limited. Attrition Bias: Low. Attrition was 10% or less. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Results are most applicable to children and adolescents 12 and older who are white. Intervention: Dasiglucagon was an appropriate dose as determined in phase 2 studies. Comparator: Comparative analysis between dasiglucagon and GlucaGen would provide data for place in therapy. Outcomes: Outcomes were appropriate to determine glucose recovery. Setting: Five sites in Germany, Slovenia, and the United States

Abbreviations: ARR = absolute risk reduction; DB = double-blind; CI = confidence interval; HbA1c = hemoglobin A1c; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NR = not reported; NNH = number needed to harm; NNT = number needed to treat; PG = parallel group; PP = per protocol; T1DM = Type 1 Diabetes Mellitus
Key: * Defined as a plasma glucose increase of 20 mg/dL or higher from baseline without rescue intravenous glucose; † Active control; ‡ Confidence intervals not provided

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
glucagon	BAQSIMI	SPRAY	NS	Y
glucagon	GLUCAGEN	VIAL	IJ	Y
glucagon	GLUCAGON EMERGENCY KIT	VIAL	IJ	Y
dasiglucagon HCl	ZEGALOGUE AUTOINJECTOR	AUTO INJCT	SQ	N
dasiglucagon HCl	ZEGALOGUE SYRINGE	SYRINGE	SQ	N
glucagon	GVOKE HYPOPEN 1-PACK	AUTO INJCT	SQ	N
glucagon	GVOKE HYPOPEN 2-PACK	AUTO INJCT	SQ	N
glucagon	GVOKE PFS 1-PACK SYRINGE	SYRINGE	SQ	N
glucagon	GVOKE PFS 2-PACK SYRINGE	SYRINGE	SQ	N
glucagon HCl	GLUCAGON EMERGENCY KIT	VIAL	IJ	
glucagon HCl	GLUCAGON HCL	VIAL	IJ	

Appendix 2: Abstracts of Comparative Clinical Trials

Dasiglucagon, a next-generation glucagon analogue, for treatment of severe hypoglycemia via an autoinjector device: Results of a phase 3, randomized, double-blind trial

Bailey TS, Willard J, Klaff LJ, Yager Stone J, Melgaard A, et al.

Abstract

Aim: To confirm the efficacy and safety of dasiglucagon when administered via an autoinjector device.

Materials and methods: In this double-blind trial, 45 participants with type 1 diabetes were randomized 3:1 to receive a single subcutaneous dose of dasiglucagon 0.6 mg or placebo following controlled induction of hypoglycaemia. The primary endpoint was time to plasma glucose recovery, defined as a plasma glucose increase of 20 mg/dL or higher from baseline without rescue intravenous glucose.

Results: Median (95% CI) observed time to recovery was 10.0 (8.0; 12.0) minutes for dasiglucagon and 35.0 (20.0; -) minutes for placebo (P < .001). Plasma glucose recovery was achieved within 15 minutes by 88% of participants receiving dasiglucagon versus none receiving placebo (P < .01). Site of injection (buttock or deltoid) was not shown to have any effect on time to recovery (P = .84). No serious adverse events occurred. As expected for glucagon treatment, nausea and vomiting were common adverse events in dasiglucagon-treated participants.

Conclusions: Dasiglucagon provided rapid reversal of hypoglycaemia in adults with type 1 diabetes. Dasiglucagon administration was well tolerated. The aqueous formulation of dasiglucagon in a ready-to-use autoinjector device that can be carried at room temperature may provide a reliable treatment for severe hypoglycaemia.

Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: Results of a phase 3, randomized controlled trial

Battelino T, Tehranchi R, Bailey T, Dovc K, Melgaard A, et al.

Abstract

Background: Dasiglucagon, a next-generation, ready-to-use aqueous glucagon analog formulation, has been developed to treat severe hypoglycemia in individuals with diabetes.

Objective: The aim of this trial was to evaluate the safety and efficacy of dasiglucagon in pediatric individuals with type 1 diabetes (T1DM). Participants were children and adolescents (6-17 years) with T1DM.

Methods: In this randomized double-blind trial, 42 participants were randomly allocated (2:1:1) to a single subcutaneous (SC) injection of dasiglucagon (0.6 mg), placebo, or reconstituted glucagon (GlucaGen; dosed per label) during insulin-induced hypoglycemia. The primary endpoint was time to plasma glucose (PG) recovery (first PG increase ≥20 mg/dL after treatment initiation without rescue intravenous glucose). The primary comparison was dasiglucagon vs. placebo; glucagon acted as a reference.

Results: The median time (95% confidence interval) to PG recovery following SC injection was 10 min (8-12) for dasiglucagon vs. 30 min (20 to -) for placebo (P < .001); the median time for glucagon was 10 min (8-12), which did not include the time taken to reconstitute the lyophilized powder. PG recovery was achieved in all participants in the dasiglucagon and glucagon groups within 20 min of dosing compared to 2 out of 11 patients (18%) with placebo. The most frequent adverse events were nausea and vomiting, as expected with glucagon treatment.

Conclusions: Consistent with adult phase 3 trials, dasiglucagon rapidly and effectively restored PG levels following insulin-induced hypoglycemia in children and adolescents with T1DM, with an overall safety profile similar to glucagon.

Dasiglucagon: A Next-Generation Glucagon Analog for Rapid and Effective Treatment of Severe Hypoglycemia Results of Phase 3 Randomized Double-Blind Clinical Trial

Pieber T, Aronson R , Hövelmann U, Willard J, et al

Abstract

Objective: To evaluate the efficacy and safety of dasiglucagon, a ready-to-use, next-generation glucagon analog in aqueous formulation for subcutaneous dosing, for treatment of severe hypoglycemia in adults with type 1 diabetes.

Research Design and Methods: This randomized, double-blind trial included 170 adult participants with type 1 diabetes, each randomly assigned to receive a single subcutaneous dose of 0.6 mg dasiglucagon, placebo, or 1 mg reconstituted glucagon (2:1:1 randomization) during controlled insulin-induced hypoglycemia. The primary end point was time to plasma glucose recovery, defined as an increase of ≥20 mg/dL from baseline without rescue intravenous glucose. The primary comparison was dasiglucagon versus placebo; reconstituted lyophilized glucagon was included as reference.

Results: Median (95% CI) time to recovery was 10 (10, 10) minutes for dasiglucagon compared with 40 (30, 40) minutes for placebo ($P < 0.001$); the corresponding result for reconstituted glucagon was 12 (10, 12) minutes. In the dasiglucagon group, plasma glucose recovery was achieved within 15 min in all but one participant (99%), superior to placebo (2%; $P < 0.001$) and similar to glucagon (95%). Similar outcomes were observed for the other investigated time points at 10, 20, and 30 min after dosing. The most frequent adverse effects were nausea and vomiting, as expected with glucagon treatment.

Conclusions: Dasiglucagon provided rapid and effective reversal of hypoglycemia in adults with type 1 diabetes, with safety and tolerability similar to those reported for reconstituted glucagon injection. The ready-to-use, aqueous formulation of dasiglucagon offers the potential to provide rapid and reliable treatment of severe hypoglycemia.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 06, 2021

Search Strategy:

#	Searches	Results
1	Glucagon/ or glucagon.mp.	49923
2	dasiglucagon.mp.	16
3	1 or 2	49927
4	limit 3 to (english language and humans and yr="2019 -Current")	2494
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	193

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZEGALOGUE® safely and effectively. See full prescribing information for ZEGALOGUE.

ZEGALOGUE (dasiglucagon) injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

ZEGALOGUE is an antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above. (1)

DOSAGE AND ADMINISTRATION

- ZEGALOGUE autoinjector and prefilled syringe are for subcutaneous injection only. (2.1)
- The dose in adults and pediatric patients aged 6 years and older is 0.6 mg. (2.2)
- Administer ZEGALOGUE according to the printed instructions on the protective case label and the Instructions For Use. (2.1)
- Visually inspect ZEGALOGUE prior to administration. The solution should appear clear, colorless, and free from particles. If the solution is discolored or contains particulate matter, do not use. (2.1)
- Administer the injection into the lower abdomen, buttocks, thigh, or outer upper arm. (2.1)
- Call for emergency assistance immediately after administering the dose. (2.1)
- If there has been no response after 15 minutes, an additional dose of ZEGALOGUE from a new device may be administered while waiting for emergency assistance. (2.1)
- When the patient has responded to treatment, give oral carbohydrates. (2.1)
- Do not attempt to reuse ZEGALOGUE. Each device contains a single dose of dasiglucagon and cannot be reused. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection:

- 0.6 mg/0.6 mL single-dose autoinjector (3)
- 0.6 mg/0.6 mL single-dose prefilled syringe (3)

CONTRAINDICATIONS

Pheochromocytoma (4)
Insulinoma (4)

WARNINGS AND PRECAUTIONS

- *Substantial Increase in Blood Pressure in Patients with Pheochromocytoma:* Contraindicated in patients with pheochromocytoma because ZEGALOGUE may stimulate the release of catecholamines from the tumor. (4, 5.1)
- *Hypoglycemia in Patients with Insulinoma:* In patients with insulinoma, administration may produce an initial increase in blood glucose, but ZEGALOGUE may stimulate exaggerated insulin release from an insulinoma and cause subsequent hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of ZEGALOGUE, give glucose orally or intravenously. (4, 5.2)
- *Hypersensitivity and Allergic Reactions:* Allergic reactions have been reported with glucagon products and may include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. (5.3)
- *Lack of Efficacy in Patients with Decreased Hepatic Glycogen:* ZEGALOGUE is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for ZEGALOGUE to be effective. Patients with these conditions should be treated with glucose. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) associated with ZEGALOGUE are:
Adults: nausea, vomiting, headache, diarrhea, and injection site pain
Pediatrics: nausea, vomiting, headache, and injection site pain (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Zealand Pharma A/S at 1-877-501-9342or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- *Beta-blockers:* Patients taking beta-blockers may have a transient increase in pulse and blood pressure. (7)
- *Indomethacin:* In patients taking indomethacin, ZEGALOGUE may lose its ability to raise blood glucose or may produce hypoglycemia. (7)
- *Warfarin:* ZEGALOGUE may increase the anticoagulant effect of warfarin. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised 03/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with type 1 or type 2 diabetes
Intervention	Glucagon therapies (e.g., spray, vial, auto-injector)
Comparator	Placebo or active control
Outcomes	Normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms
Timing	As needed for hypoglycemia
Setting	Outpatient