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Drug Class Review: Diabetes, Glucagon

Date of Review: February 2020 **End Date of Literature Search:** 11/26/2019

Purpose for Class Review:
The purpose of this class review is to create a glucagon class on the preferred drug list (PDL) and evaluate evidence for glucagon products to determine PDL status.

Research Questions:
1. What is the comparative efficacy and effectiveness of different glucagon formulations to reverse severe hypoglycemia in patients with diabetes mellitus?
2. What is the comparative tolerability and harms of different glucagon formulations when used to treat severe hypoglycemia in patients with diabetes mellitus?
3. Are there subpopulations of patients based on demographics (e.g., age, gender, race) or comorbidities (e.g., drug-disease interactions, obesity) with diabetes mellitus for which a specific glucagon formulation may be more effective or associated with less harm?

Conclusions:
- There is a paucity of high-quality evidence for any of the glucagon products used for the treatment of hypoglycemia. There is insufficient comparative evidence between the different glucagon formulations. One high-quality clinical practice guideline and 2 randomized controlled trials (RCT) were included in the review.
- A guideline from the National Institute for Health and Care Excellence (NICE) for the management of type 1 diabetes (T1DM) recommends intramuscular (IM) glucagon for the treatment of severe hypoglycemia (intranasal glucagon was not available at the time of the NICE review).[1]
- Glucagon nasal powder was found to be non-inferior to IM glucagon in a study of adult patients with T1DM (n=75).[2] Treatment success (defined as an increase in plasma glucose to 70 mg/dL or more, or an increase of at least 20 mg/dL from glucose nadir within in 30 minutes of receiving glucagon) was experienced by 98.7% of patients randomized to intranasal glucagon compared to 100% of patients given IM glucagon.[2]

Recommendations:
- Create a PDL class for the glucagon products.
- After evaluation of costs in executive session, a new PDL class is created with GlucaGen®, Glucagon emergency kit, and Baqsimi™ spray as preferred agents, Gvoke™ formulation is non-preferred.

Background:
Hypoglycemia requiring treatment is most commonly experienced in patients with T1DM and type 2 diabetes (T2DM) who use antidiabetic therapies to normalize glucose levels.[3] 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. 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.[4] 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.[3]

Hypoglycemia can be defined as severe hypoglycemia (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).[3,4]

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.[5,6] Fifteen grams of glucose is required to increase blood glucose levels approximately 37 mg/dL within 20 minutes.[7] Administration of glucagon is required in patients with severe hypoglycemia who are not being treated in a medical setting.[3,5] Glucagon stimulates endogenous glucose production to increase blood glucose levels. Glucagon given subcutaneously (SQ) or IM increases blood glucose 54 mg/dL to 216 mg/dL in 60 minutes.[7] It is recommended that patients with T1DM always carry a form of glucagon (subcutaneous, intramuscular or nasal) that can be administered by a caregiver if needed.[1]

The 4 glucagon formulations available in the U.S. are outlined in **Table 1**. [8–11] Reconstituted glucagon products can be given SQ, IM or IV and products that are ready to use are administered SQ only. Nasal glucagon is administered intranasally via a device which dispenses a glucagon powder that is readily absorbed by the mucous membrane.[3] 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. Glucagon Products

Brand	Formulation	Reconstitution	Route
Baqsimi™	spray	No	Nasal
Glucagen®	vial	Yes	SQ, IM or IV
Glucagon Emergency Kit	vial	Yes	SQ, IM or IV
Gvoke Hypopen™	auto injection	No	SQ
Gvoke Syringe™	syringe	No	SQ
Abbreviations: IM – intramuscular; IV – intravenous; SQ – subcutaneously			

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 (Appendix 3).

In Quarter 3 of 2019 there were 50 claims for glucagon products for Oregon Health Plan (OHP) fee-for-service (FFS) patients. Most prescription claims were for glucagon kits; however, intranasal glucagon and pre-filled syringes/auto-injectors were also prescribed. Glucagon products do not currently have an assigned PDL status.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing for Glucagon Products.

Brand Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Baqsimi™[9] (Lilly)	Antihypoglycemic agent indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and older	3 mg intranasal spray powder	1 spray into 1 nostril Dose may repeat once after 15 minutes if no response
GlucaGen®[10] (Novo Nordisk)	Antihypoglycemic agent and a gastrointestinal motility inhibitor for the treatment of hypoglycemia and use as a diagnostic aid	1 mg/ 1mL SQ, 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[8] (Lilly)	Treatment for severe hypoglycemia in patients with diabetes mellitus and as a diagnostic aid	1 mg/ 1 mL SQ, 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™[11] (Xeris) Pre-filled syringe and auto-injector	Antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above	0.5 mg/0.1 mL or 1 mg/0.2 mL SQ	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

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

Table 2. Summary of Pivotal Studies Completed.

Study	Comparison	Population	Primary Outcome	Results
Rickels, et al[2] Phase 3, CO, MC, NI, RCT	Glucagon nasal powder 3 mg Vs. Intramuscular glucagon 1 mg	Adults with T1DM (n = 75)	Treatment success (increase in plasma glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from glucose nadir) within in 30 minutes of receiving glucagon	Nasal glucagon: 98.7% Intramuscular glucagon: 100% TD 1.3% (upper end of 97.5% CI, 4.0%) *Nasal glucagon was non-inferior to intramuscular glucagon*
Sherr, et al[12] Phase 1, CO, MC, RCT	Glucagon nasal powder† Vs. Intramuscular glucagon†	Youth (4 to < 17 years) patients with T1DM (n = 48)	Pharmacokinetic study achieving at least a 25 mg/dL increase in glucose above the nadir within 20 minutes of administration	Nasal glucagon: 100% Intramuscular glucagon: 100% *Nasal glucagon was equal to intramuscular glucagon in raising glucose levels*

Key: † Patients 4 years to < 8 years and 8 years to < 12 years were randomly assigned to 2 or 3 mg intranasal glucagon dose in two separate sessions or a single, weight-based dose of intramuscular glucagon.
Abbreviations: CO – cross-over; MC – multi-center; NI – non-inferiority; RCT – randomized clinical trial; T1DM – type 1 diabetes mellitus; TD – treatment difference

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 2**, 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:
After review, one systematic review was excluded due to poor quality (e.g., low-quality of evidence).[13]

Guidelines:
High Quality Guidelines:

NICE – Type 1 Diabetes in Adults

The diagnosis and management of adult patients with T1DM was updated in a 2015 clinical guideline by NICE. For the purposes of this review, only the medical interventions for hypoglycemia will be presented. Evidence from two trials found a slower recovery in patients in a hypoglycemic coma given 1 mg glucagon, IM or IV, compared to 50 mL 50% IV dextrose (evidence based on data from quasi-experimental study [IIb]).

Recommendation:

- Adults with T1DM with a decreased level of consciousness as a result of hypoglycemia and therefore unable to take oral treatment should:
    - Be given IM glucagon by a caregiver or IV glucose by a healthcare professional that is able to obtain IV access.
    - Monitored for 10 minutes and given IV glucose if consciousness is not improving.
    - Oral carbohydrates should be given when it is safe to administer and the patient should continue to be monitored for relapse.

After review, 3 guidelines were excluded due to poor quality.[4,6,7]

References:

1. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. Guidance and guidelines NICE. https://www.nice.org.uk/guidance/ng17. Accessed June 28, 2017.
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4. 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. *J Clin Endocrinol Metab*. 2013;98(5):1845-1859. doi:10.1210/jc.2012-4127.
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7. Yale J-F, Paty B, Senior PA. Hypoglycemia. *Canadian Journal of Diabetes*. 2018;42:S104-S108. doi:10.1016/j.jcjd.2017.10.010.
8. Glucagon [prescribing information]. Indianapolis, IN: Lilly, USA, LLC, April 2018.
9. Baqsimi (glucagon)[product information].Indianapolis, IN: Lilly USA, LLC, July 2019.
10. GlucaGen (glucagon) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk A/S, July 2018.
11. Gvoke (glucagon) [prescribing information]. Chilcago, IL: Xeris Pharmaceuticals, September 2019.
12. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon Nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care*. 2016;39(4):555-562. doi:10.2337/dc15-1606.
13. Boido A, Ceriani V, Pontiroli AE. Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: a systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. *Acta Diabetologica*. 2015;52(2):405-412. doi:10.1007/s00592-014-0665-0.

Appendix 1: Specific Drug Information

Generic	Brand	Form	Route
glucagon	BAQSIMI	SPRAY	NS
glucagon,human recombinant	GLUCAGEN	VIAL	IJ
glucagon,human recombinant	GLUCAGON EMERGENCY KIT	VIAL	IJ
glucagon	GVOKE HYPOPEN	AUTO INJCT	SQ
glucagon	GVOKE SYRINGE	SYRINGE	SQ

Table 3. Clinical Pharmacology and Pharmacokinetics (T1DM adult patients).

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Glucagon (Baqsimi™)[9]	Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver.	Intranasal: 6130 pg/mL	Degraded by the liver, kidney and plasma.	• Half-life: 35 minutes • Cmax: NR • AUC: NR • Vd: 885 L
Glucagon (GlucaGen®)[10]	Same as above	NA	Same as above	• Half-life: 45 minutes • Cmax: 1686 pg/mL • AUC: NR • Vd: NR
Glucagon (Emergency kit)[8]	Same as above	NA	Same as above	• Half-life: 8-18 minutes • Cmax: 7.9 ng/mL • AUC: NR • Vd: 0.25 L/kg
Glucagon (Gvoke™)[11]	Same as above	NA	Same as above	• Half-life: 32 minutes • Cmax: 2481.3 pg/mL • AUC: 3454.6 pg/mL • Vd: NR
Abbreviation: AUC – are under the curve; Cmax – maximum concentration; NA – not applicable; NR – not reported; T1DM – type 1 diabetes mellitus; VD – volume of distribution				

Use in Specific Populations: Glucagon should not be used in patients with pheochromocytoma and is contraindicated in patients with insulinoma. Patients with decreased hepatic glycogen may not respond to glucagon.

Drug Safety:
Boxed Warnings: none

Risk Evaluation Mitigation Strategy Programs: none

Contraindications: Do not use glucagon in patients with pheochromocytoma, insulinoma, or hypersensitivity to glucagon.

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Glucagon (Baqsimi™)	Glucagon (GlucaGen®)	Glucagon (Emergency kit)	Glucagon (Gvoke)
Catecholamine release in patients with pheochromocytoma	X	X	X	X
Hypoglycemia in patients with insulinoma	X		X	X
Hypersensitivity and allergic reactions	X	X	X	X
Lack of efficacy in patients with decreased hepatic glycogen	X	X	X	X
Necrolytic migratory erythema		X		X
Hypoglycemia in patients with glucagonoma				X
Caution in patients with cardiac disease		X		

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 26, 2019

Search Strategy:

#	Searches	Results
1	Glucagon/ or glucagon.mp.	47022
2	glucagon injection.mp.	218
3	glucagon spray.mp.	0
4	1 or 2 or 3	47022
5	limit 4 to (english language and humans and yr="2000 -Current")	11641
6	limit 5 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	378

Appendix 3: Key Inclusion Criteria

Population	Patients with T1DM and T2DM
Intervention	Glucagon spray, vial, and auto-injector
Comparator	Glucagon formulations by differing routes
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	Onset of hypoglycemia
Setting	Outpatient