



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Glucagon Products Review
-January 2021-



Background:

In January 2021, the National Pharmacy and Therapeutics Committee (NPTC) reviewed the currently available treatment options for severe hypoglycemia in diabetics, as well as guidelines for the treatment of hypoglycemia in diabetics, to determine if changes to the National Core Formulary (NCF) were warranted. The NCF currently lists glucagon (outpatient use only) as the named formulary agent. Following the clinical and pharmacoeconomic analyses, the NPTC voted to **ADD oral glucose, any formulation** to the NCF.

Discussion:

According to “Prevalence of diagnosed diabetes in American Indian and Alaskan Native (AI/AN) adults, 2006-2017” released in 2020, there were 729,470 patients in the IHS active clinical population in 2006, with the number increasing to 1,034,814 in 2017. Of this population, 86,245 had diagnosed diabetes in 2006, increasing to 137,594 in 2017, a diabetes prevalence rate of 14.6% in AI/AN adults. American Indians/Alaska Natives were also 2.5 times more likely than non-Hispanic whites to die from diabetes in 2017. Per the U.S. Centers for Disease Control and Prevention, 16 million emergency department (ED) visits were reported with diabetes as any listed diagnosis among adults aged 18 years or older in 2016, including 224,000 for hyperglycemic crisis (9.7 visits per 1,000 adults with diabetes) and 235,000 for hypoglycemia (10.2 visits per 1,000 adults with diabetes). In addition, a total of 7.8 million hospital discharges were reported in 2016 with diabetes as any listed diagnosis among US adults aged 18 years or older (339 visits per 1,000 adults with diabetes), of which 57,000 were for hypoglycemia (2.5 visits per 1,000 adults with diabetes).^{1,2}

American Diabetes Association (ADA) workgroups have defined hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm. In 2020, the ADA classified hypoglycemia as Levels 1-3, as follows:

- Level 1: Glucose 70 mg/dL and \geq 54 mg/dL
- Level 2: Glucose <54 mg/dL
- Level 3: A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

A blood glucose concentration of 70 mg/dL has been recognized as a threshold for neuroendocrine response to falling glucose in people without diabetes. Because many people with diabetes demonstrate impaired counter-regulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL is considered clinically important, independent of the severity of acute hypoglycemic symptoms. A blood glucose concentration <54 mg/dL is the threshold at which neuroglycopenic symptoms begin to occur and require immediate action to resolve the hypoglycemic event.³

The goal of treatment of hypoglycemia is to raise the plasma glucose concentration to normal by providing dietary or parenteral carbohydrate (specifically glucose), or in cases of severe hypoglycemia, by stimulating endogenous glucose production by administering glucagon. *In order to treat early symptoms of hypoglycemia, patients should be certain that 15-20 grams of a fast-acting carbohydrate source (such as glucose tablets, hard candy, or sweetened fruit juice) is available at all times.* The severely-symptomatic patient will require the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.⁴

There are multiple glucagon delivery device mechanisms with current FDA approval for the treatment of severe hypoglycemia in patients with diabetes. Along with the well-known reconstitutable glucagon emergency kits, several alternative delivery device mechanisms received FDA approval in 2019. The current FDA-approved glucagon delivery devices include an intranasal nasal spray, subcutaneous (SC) or intramuscular (IM) reconstitutable vials, a SC auto-injector pen, and a SC prefilled syringe. The glucagon SC or IM reconstitutable vial kits are approved for use in all age groups, the SC auto-injector pen and SC

prefilled syringe are approved for ages two years and older, and the intranasal glucagon powder spray is approved for ages four years and older.⁵

A review was conducted of three open-label, crossover, non-inferiority randomized controlled trials (RCTs) and one quasi-blinded, quasi-crossover RCT for safety and efficacy of glucagon products. All four RCTs included experimentally-induced hypoglycemia with insulin. There were 273 patients enrolled across the four studies (225 adults and 48 children aged 4 to 16 years old). Inclusion criteria for all RCTs included a diagnosis of diabetes and current insulin use. Exclusion criteria included severe hypoglycemia needing assistance prior to study start. Glucagon delivery forms included intranasal glucagon and IM glucagon. The primary endpoint was response to glucagon, defined as an increase in plasma glucose to ≥ 3.9 mmol/L or an increase of ≥ 1.1 mmol/L from nadir within 30 minutes of glucagon dose, with no additional actions with a non-inferiority margin of 10%. Compared to IM glucagon, patients receiving intranasal glucagon for hypoglycemia have similar rates of treatment success but a longer time for recovery to normal glycaemia and recovery from symptoms of hypoglycemia.⁶

A cross-sectional, qualitative research study was reviewed comparing perceptions of glucagon delivery devices and included comparison of intranasal glucagon to SC glucagon auto-injector. A total of 21,621 respondents were reached via email to assess their interest and only 45 were found eligible for this study. A total of 45 (15 patients, 15 caregivers, and 15 acquaintances) interviews were conducted (mean ages, 55, 40, and 51, respectively) between October 8-26th, 2018. More participants across all subgroups preferred nasal glucagon (33 [73%]) versus auto-injector glucagon (12 [27%]). The most frequent reasons for preferring nasal glucagon included ease of use, absence of a needle, not needing to move or remove clothing to find an injection site, and a higher general level of comfort with it.

The 2020 American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommendations state that glucose (15–20 grams) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL, although any form of carbohydrate that contains glucose may be used. Providers should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL or less. Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL, so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. The ADA also states that glucagon administration is not limited to health care professionals, particularly with the availability of intranasal and stable soluble glucagon available in auto-injector pens.³

Findings:

Oral glucose agents remain the guideline-supported, first-line staple in the treatment of hypoglycemia for the symptomatic, non-severe patient. For the severely symptomatic patient, glucagon remains the guideline-supported, first-line staple in the treatment of hypoglycemia. Evidence from published literature, guidelines, and internal pharmaco-economic analyses offers a value-based decision opportunity which supports the addition of “oral glucose, any formulation” to the IHS National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

1. Bullock A, Sheff K, Hora, I, et al. [Prevalence of diagnosed diabetes in American Indian and Alaskan Native adults, 2006-2017](#). *BMJ Open Diab Res Care*. 2020; 8:e001218.
2. U.S. Centers for Disease Control and Prevention. [National Diabetes Statistics Report, 2020](#). Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
3. American Diabetes Association. [Standards of Medical Care in Diabetes, 2020](#). *Diabetes Care* 2020; 43:S66–S76.
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.
5. Oregon State University, Oregon Health Authority. [Drug Class Review: Diabetes, Glucagon](#). February 2020.
6. Canadian Agency for Drugs and Technologies in Health. [Common Drug Review. Clinical Review Report: Glucagon nasal powder \(Baqsimi\)](#). March 2020.
7. Bajpai SK, Cambron MJ, Peck E, et al., Perceptions About Glucagon Delivery Devices for Severe Hypoglycemia: Qualitative Research With Patients, Caregivers, and Acquaintances. *Clin Ther*. 2019; 41(10):2073-2089.