HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GlucaGen® (glucagon) for injection, for subcutaneous, intramuscular or intravenous use
Initial U.S. Approval: 1960

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2)----------03/2021
Contraindications (4)----------03/2021
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7, 5.8)----------03/2021

----------INDICATIONS AND USAGE----------
GlucaGen is an antihypoglycemic agent and a gastrointestinal motility inhibitor indicated:

- for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes (1.1)
- as a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in adult patients (1.2)

----------DOSAGE AND ADMINISTRATION----------
Dosage in adults and pediatric patients using the GlucaGen HypoKit to treat severe hypoglycemia (2.2)

- Adults and Pediatric Patients Weighing 25 kg or More or for Pediatric Patients with Unknown Weight 6 Years and Older:
  -The recommended dosage is 1 mg (1 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.
  -If there has been no response after 15 minutes, an additional 1 mg dose (1 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.
- Pediatric Patients Weighing Less Than 25 kg or for Pediatric Patients with Unknown Weight Less Than 6 Years of Age:
  -The recommended dosage is 0.5 mg (0.5 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.
  -If there has been no response after 15 minutes, an additional 0.5 mg dose (0.5 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

Important Administration Instructions for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia (2.1)

- GlucaGen is for subcutaneous, intramuscular, or intravenous injection. Administer intravenously ONLY under medical supervision.
- See the Full Prescribing Information for administration instructions

Dosage in Adults for Using GlucaGen Diagnostic Kit and GlucaGen 10-pack as a Diagnostic Aid (2.4)

- The recommended diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum, and small bowel is 0.2 mg to 0.5 mg administered intravenously or 1 mg administered intramuscularly; the recommended dose to relax the colon is 0.5 mg to 0.75 mg administered intravenously or 1 mg to 2 mg administered intramuscularly.
- See the Full Prescribing Information for administration instructions (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection (3):
Treatment of Severe Hypoglycemia:
1 mg single-dose vial of GlucaGen with a 1 mL single-dose syringe of Sterile Water for Injection, USP (GlucaGen HypoKit®)
Use as a Diagnostic Aid:
1 mg single-dose vial of GlucaGen
1 mg single-dose vial of GlucaGen with a 1 mL single-dose vial of Sterile Water for Injection, USP (Diagnostic Kit)

----------CONTRAINDICATIONS----------

- Pheochromocytoma (4)
- Insulinoma (4)
- Known hypersensitivity to glucagon or to any of the excipients (4)
- Glucagonoma when used as a diagnostic aid (4)

----------WARNINGS AND PRECAUTIONS----------
Substantial Increase in Blood Pressure in Patients with Pheochromocytoma: Contraindicated in patients with pheochromocytoma because GlucaGen 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; however, GlucaGen may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of GlucaGen, give glucose orally or intravenously. (4, 5.2)
Hypersensitivity and Allergic Reactions: Allergic reactions have been reported and include generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. (4, 5.3)
Lack of Efficacy in Patients with Decreased Hepatic Glycogen: GlucaGen 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 GlucaGen to be effective. Patients with these conditions should be treated with glucose. (5.4)
Necrolytic Migratory Erythema (NME): a skin rash, has been reported postmarketing following continuous glucagon infusion and resolved with discontinuation of the glucagon. Should NME occur, consider whether the benefits of continuous glucagon infusion outweigh the risks. (5.5)
Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid: Treatment with GlucaGen in patients with diabetes mellitus may cause hyperglycemia. Monitor diabetic patients for changes in blood glucose levels during treatment and treat if indicated. (5.6)
Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when Used as a Diagnostic Aid: GlucaGen may increase myocardial oxygen demand, blood pressure, and pulse rate. Cardiac monitoring is recommended in patients with cardiac disease during use of GlucaGen as a diagnostic aid, and an increase in blood pressure and pulse rate may require therapy. (5.7)
Hypoglycemia in Patients with Glucagonoma:
Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Test patients suspected of having glucagonoma for blood levels of glucagon prior to treatment. (5.8)

----------ADVERSE REACTIONS----------
Glucagon adverse reactions identified during post approval use are: injection site reactions, nausea, vomiting, headache, dizziness, asthenia, pallor, diarrhea, somnolence, and decreased blood pressure.(6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or 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. (7.1)
Indomethacin: In patients taking indomethacin GlucaGen may lose its ability to raise glucose or may produce hypoglycemia. (7.2)
Anticholinergic drugs: Concomitant use of anticholinergic drugs with GlucaGen for use as a diagnostic aid is not recommended. (7.3)
Warfarin: GlucaGen may increase the anticoagulant effect of warfarin. (7.4)
Insulin: Monitor blood glucose when GlucaGen is used as a diagnostic aid in patients receiving insulin. (7.5)

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

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Severe Hypoglycemia

GlucaGen is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes.

1.2 Diagnostic Aid

GlucaGen is indicated as a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia

GlucaGen is for subcutaneous, intramuscular, or intravenous injection. Administer intravenously ONLY under medical supervision.

Instruct patients and their caregivers on the signs and symptoms of severe hypoglycemia. Because severe hypoglycemia requires the help of others to recover, instruct the patient to inform those around them about GlucaGen and its Instructions for Use. Administer GlucaGen as soon as possible when severe hypoglycemia is recognized.
Instruct the patient or caregiver to read the Instructions for Use at the time they receive a prescription for GlucaGen. Emphasize the following instructions to the patient or caregiver:

- Using the supplied prefilled syringe, carefully insert the needle through the rubber stopper of the vial containing GlucaGen powder and inject all the liquid from the syringe into the vial.
- Shake the vial gently until the powder is completely dissolved and no particles remain in the fluid. The reconstituted solution should be clear and colorless. Inspect visually for particulate matter and discoloration. If the resulting solution is cloudy or contains particulate matter do not use.
- The reconstituted solution is 1 mg per mL glucagon.
- Immediately after reconstitution, using the same syringe, withdraw the correct dose of GlucaGen.
- Inject the solution subcutaneously or intramuscularly in the upper arm, thigh, or buttocks. In addition, healthcare providers may administer intravenously.
- Call for emergency assistance immediately after administering the dose.
- If there has been no response after 15 minutes, an additional dose of GlucaGen may be administered while waiting for emergency assistance.
- When the patient has responded to the treatment and is able to swallow, give oral carbohydrates to restore the liver glycogen and prevent recurrence of hypoglycemia.
- Discard any unused portion.

2.2 Dosage in Adults and Pediatric Patients for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia

Adults and Pediatric Patients Weighing 25 kg or More or for Pediatric Patients with Unknown Weight 6 Years and Older

- The recommended dosage is 1 mg (1 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.

- If there has been no response after 15 minutes, an additional 1 mg dose (1 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

Pediatric Patients Weighing Less Than 25 kg or for Pediatric Patients with Unknown Weight Less Than 6 Years of Age

- The recommended dosage is 0.5 mg (0.5 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.

- If there has been no response after 15 minutes, an additional 0.5 mg dose (0.5 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

For GlucaGen Diagnostic Kit and the GlucaGen 10-pack:

2.3 Important Administration Instruction for Using GlucaGen Diagnostic Kit and the GlucaGen 10-pack as a Diagnostic Aid

- Reconstitute GlucaGen with 1 mL of Sterile Water for Injection. Using a syringe, withdraw all of the Sterile Water for Injection (if supplied) or 1 mL Sterile Water for Injection and inject into the GlucaGen vial.

- Shake the vial gently until the powder is completely dissolved and no particles remain in the fluid. The reconstituted fluid should be clear and colorless. Inspect visually for particulate matter and discoloration. If the resulting solution is cloudy or contains particulate matter do not use.

- The reconstituted solution is 1 mg per mL glucagon.

- Immediately after reconstitution, inject the solution intravenously or intramuscularly into upper arm, thigh, or buttocks.

- Discard any unused portion.

- After the end of the diagnostic procedure, give oral carbohydrates to patients who have been fasting, if this is compatible with the diagnostic procedure.

2.4 Dosage in Adults for Using GlucaGen Diagnostic Kit and GlucaGen for Injection Single-Dose Vial as a Diagnostic Aid

- The recommended diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum, and small bowel is 0.2 mg to 0.5 mg administered intravenously or 1 mg administered intramuscularly; the recommended dose to relax the colon is 0.5 mg to 0.75 mg administered intravenously or 1 mg to 2 mg administered intramuscularly *[see Clinical Pharmacology (12.2)]*.

- The onset of action after an injection will depend on the organ under examination and route of administration *[see Clinical Pharmacology (12.2)]*.

3 DOSAGE FORMS AND STRENGTHS

GlucaGen for injection is a white lyophilized powder supplied as follows:

Treatment of Severe Hypoglycemia

- 1 mg single-dose vial of GlucaGen with a 1 mL single-dose syringe of Sterile Water for Injection, USP (GlucaGen HypoKit®)

Use as a Diagnostic Aid

- 1 mg single-dose vial of GlucaGen
- 1 mg single-dose vial of GlucaGen with a 1 mL single-dose vial of Sterile Water for Injection, USP (Diagnostic Kit)

4 CONTRAINDICATIONS

GlucaGen is contraindicated in patients with:

- Pheochromocytoma because of the risk of substantial increase in blood pressure [*see Warnings and Precautions (5.1)*]
- Insulinoma because of the risk of hypoglycemia [*see Warnings and Precautions (5.2)*]
- Known hypersensitivity to glucagon or the excipients in GlucaGen. Allergic reactions have been reported with glucagon and include anaphylactic shock with breathing difficulties and hypotension *[see Warnings and Precautions (5.3)]*
- Glucagonoma when used as a diagnostic aid because of risk of hypoglycemia *[see Warnings and Precautions (5.8)]*

5 WARNINGS AND PRECAUTIONS

5.1 Substantial Increase in Blood Pressure in Patients with Pheochromocytoma

GlucaGen is contraindicated in patients with pheochromocytoma because GlucaGen may stimulate the release of catecholamines from the tumor *[see Contraindications (4)]*. If the patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure for the short time that control would be needed.

5.2 Hypoglycemia in Patients with Insulinoma

In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, GlucaGen administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. GlucaGen is contraindicated in patients with insulinoma *[see Contraindications (4)]*. If a patient develops symptoms of hypoglycemia after a dose of GlucaGen, give glucose orally or intravenously.

5.3 Hypersensitivity and Allergic Reactions

Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. GlucaGen is contraindicated in patients with a prior hypersensitivity reaction *[see Contraindications (4)]*.

5.4 Lack of Efficacy in Patients with Decreased Hepatic Glycogen

GlucaGen 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 GlucaGen administration to be effective. Patients with these conditions should be treated with glucose.

5.5 Necrolytic Migratory Erythema

Necrolytic migratory erythema (NME), a skin rash commonly associated with glucagonomas (glucagon-producing tumors) and characterized by scaly, pruritic erythematous plaques, bullae, and erosions, has been reported postmarketing following continuous glucagon infusion. NME lesions may affect the face, groin, perineum and legs or be more widespread. In the reported cases NME resolved with discontinuation of the glucagon, and treatment with corticosteroids was not effective. Should NME occur, consider whether the benefits of continuous glucagon infusion outweigh the risks.

5.6 Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid

Treatment with GlucaGen in patients with diabetes mellitus may cause hyperglycemia. Monitor diabetic patients for changes in blood glucose levels during treatment and treat if indicated.

5.7 Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when used as a Diagnostic Aid

GlucaGen may increase myocardial oxygen demand, blood pressure, and pulse rate which may be life-threatening in patients with cardiac disease. Cardiac monitoring is recommended in patients with cardiac disease during use of GlucaGen as a diagnostic aid, and an increase in blood pressure and pulse rate may require therapy.

5.8 Hypoglycemia in Patients with Glucagonoma

Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Test patients suspected of having glucagonoma for blood levels of glucagon prior to use as a diagnostic aid as GlucaGen is contraindicated in this setting *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity and Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Necrolytic Migratory Erythema *[see Warnings and Precautions (5.5)]*
- Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid *[see Warnings and Precautions (5.6)]*
- Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when Used as a Diagnostic Aid *[see Warnings and Precautions (5.7)]*

The following adverse reactions have been identified during post-approval use of glucagon. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Injection site reactions
- Nausea
- Vomiting
- Headache
- Dizziness
- Asthenia
- Pallor
- Diarrhea
- Somnolence
- Generalized allergic reactions including anaphylactic shock with breathing difficulties and hypotension

- Hypertension and tachycardia
- Decreased blood pressure. Hypotension has been reported up to 2 hours after administration in patients receiving GlucaGen as premedication for upper gastrointestinal endoscopy procedures.
- Hypoglycemia and hypoglycemic coma. Patients taking indomethacin may be more likely to experience hypoglycemia following glucagon administration *[see Drug Interactions (7)]*.
- Necrolytic Migratory Erythema (NME) cases have been reported post marketing in patients receiving continuous infusion of glucagon.

7 DRUG INTERACTIONS

Table 1: Clinically Significant Drug Interactions with GlucaGen

Beta-Blockers	
Clinical Impact:	Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given GlucaGen.
Intervention:	The increase in blood pressure and heart rate may require therapy in patients with coronary artery disease.
Indomethacin	
Clinical Impact:	In patients taking indomethacin, GlucaGen may lose its ability to raise blood glucose or may even produce hypoglycemia.
Intervention:	Monitor blood glucose levels during GlucaGen treatment of patients taking indomethacin.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs and GlucaGen increase the risk of gastrointestinal adverse reactions due to additive effects on inhibition of gastrointestinal motility.
Intervention:	Concomintant use of anticholinergic drugs with GlucaGen for use as a diagnostic aid is not recommended.
Warfarin	
Clinical Impact:	GlucaGen may increase the anticoagulant effect of warfarin.
Intervention:	Monitor patients for unusual bruising or bleeding, as adjustments in warfarin dosage may be required.
Insulin	
Clinical Impact:	Insulin acts antagonistically to glucagon.
Intervention:	Monitor blood glucose when GlucaGen is used as a diagnostic aid in patients receiving insulin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Multiple small studies have

demonstrated a lack of transfer of pancreatic glucagon across the human placental barrier during early gestation. In rat and rabbit reproduction studies, no embryofetal toxicity was observed with glucagon administered by injection during the period of organogenesis at doses representing up to 100 and 200 times the human dose, respectively, based on body surface area (mg/m^2) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In rats and rabbits given glucagon by injection at doses of 0.4, 2, and 10 mg/kg (up to 100 and 200 times the human dose based on mg/m^2 for rats and rabbits, respectively) there was no evidence of increased malformations or embryofetal lethality.

8.2 Lactation

Risk Summary

There is no information available on the presence of glucagon in human or animal milk, the effects of glucagon on the breastfed child or the effects of glucagon on milk production. However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore, unlikely to cause harm to an exposed infant.

8.4 Pediatric Use

The safety and effectiveness of GlucaGen for the treatment of severe hypoglycemia in pediatric patients with diabetes have been established.

Safety and effectiveness for use as a diagnosic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in pediatric patients have not been established.

10 OVERDOSAGE

If overdosage occurs, the patient may experience nausea, vomiting, inhibition of gastrointestinal tract motility, increase in blood pressure and pulse rate. In case of suspected overdosing, the serum potassium may decrease and should be monitored and corrected if needed. If the patient develops a dramatic increase in blood pressure, phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

11 DESCRIPTION

Glucagon is an antihypoglycemic agent and a gastrointestinal motility inhibitor. It is produced by expression of recombinant DNA in a *Saccharomyces cerevisiae* vector with subsequent purification. The chemical structure of the glucagon is identical to human glucagon. Glucagon with the empirical formula of $C_{153}H_{225}N_{43}O_{49}S$, and a molecular weight of 3483, is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-
1 2 3 4 5 6 7 8 9 10 11

Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
12 13 14 15 16 17 18 19 20 21 22

Val-Gln-Trp-Leu-Met-Asn-Thr
23 24 25 26 27 28 29

GlucaGen is a sterile, lyophilized white powder for reconstitution for subcutaneous, intramuscular or intravenous use, supplied in a 2 mL vial (appearance of the powder may vary, and occasionally the powder may appear compacted). Each vial for reconstitution contains 1 mg of glucagon, 107 mg of lactose monohydrate, hydrochloric acid and sodium hydroxide. Hydrochloric acid and/or sodium hydroxide may be used to adjust the pH before lyophilization. The reconstituted solution of GlucaGen contains glucagon 1 mg/mL at pH 2.5-3.5, and is soluble in water.

12 CLINICAL PHARMACOLOGY

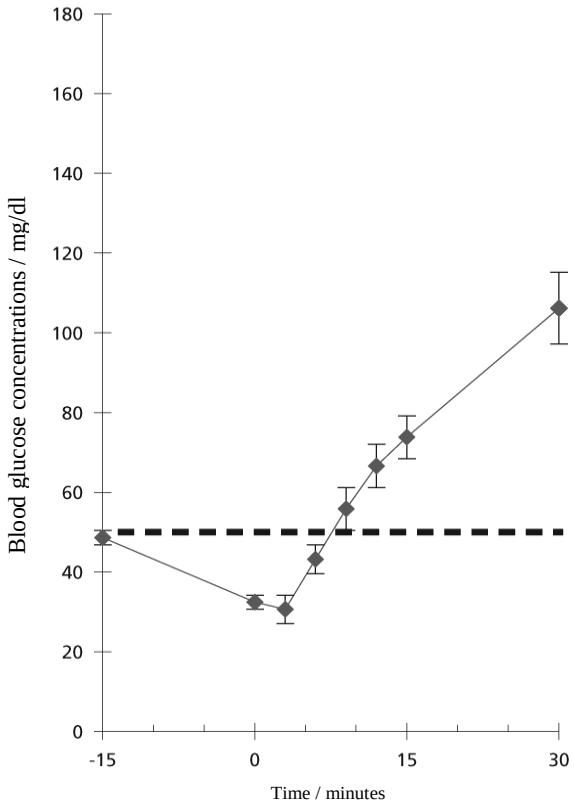
12.1 Mechanism of Action

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect. Extrahepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon.

12.2 Pharmacodynamics

Treatment of Severe Hypoglycemia:
Blood glucose concentration rises within 10 minutes of injection and maximal concentrations are attained at approximately 30 minutes after injection (see Figure 1). The duration of hyperglycemic action after intravenous or intramuscular injection is 60-90 minutes.

Figure 1. Recovery from Insulin Induced Hypoglycemia (mean blood glucose) after Intramuscular Injection of 1 mg GlucaGen in Type 1 Diabetic Men



Diagnostic Aid:

Table 2: Pharmacodynamic Properties of Glucagon for Intravenous Route

Route of Administration	Dose[a]	Time of Maximal Glucose Concentration	Time of Onset of Action for GI Smooth Muscle Relaxation	Duration of Smooth Muscle Relaxation
Intravenous	0.25 to 0.5 mg	5 to 20 minutes	45 seconds	9 to 17 minutes

[a]Dose is determined based on the length of the procedure.

Table 3: Pharmacodynamic Properties of GlucaGen for Intramuscular Route

Route of Administration	Dose[a]	Time of Maximal Glucose Concentration	Time of Onset of Action for GI Smooth Muscle Relaxation	Duration of Smooth Muscle Relaxation
Intramuscular	1 mg	30 minutes	8 to 10 minutes	12 to 27 minutes
	2 mg	30 minutes	4 to 7 minutes	21 to 32 minutes

[a]Dose is determined based on the length of the procedure.

The time of maximal glucose concentration for GlucaGen administered subcutaneously is 30-45 minutes.

12.3 Pharmacokinetics

Absorption

Intramuscular injection of 1 mg GlucaGen resulted in a mean C_{max} (CV%) of 1686 pg/mL (43%) and median T_{max} of 12.5 minutes.

Elimination

The mean apparent half-life of 45 minutes after intramuscular injection probably reflects prolonged absorption from the injection site.

Metabolism

Glucagon is degraded in the liver, kidney, and plasma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals to evaluate carcinogenic potential have not been performed.

Mutagenesis

The mutagenic potential tested in the Ames and human lymphocyte assays, was borderline positive under certain conditions for both glucagon (pancreatic) and glucagon (rDNA) origin. Doses of 100 and 200 mg/kg of glucagon of both pancreatic and recombinant origins gave slightly higher incidences of micronucleus formation in male mice but there was no effect in females. The weight of evidence indicates that synthetic and recombinant glucagon are not different and do not pose a genotoxic risk to humans

Impairment of Fertility

Glucagon was not tested in animal fertility studies. Studies in rats have shown that pancreatic glucagon does not cause impaired fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

GlucaGen for injection is supplied as a lyophilized white powder available as follows:

Presentation	NDC	Strength	Description
Treatment of Severe Hypoglycemia			
GlucaGen HypoKit	0169-7065-15	1 mg per vial	1 mL single-dose vial of GlucaGen with 1 mL single-dose syringe of

			Sterile Water for Injection, USP for reconstitution
Use as a Diagnostic Aid			
GlucaGen 10-pack: 10 Single-dose vials	0597-0053-45	1 mg per vial	1 mL single-dose vial of GlucaGen
GlucaGen Diagnostic Kit	0597-0260-10	1 mg per vial	1 mL single-dose vial of GlucaGen with 1 mL single-dose vial of Sterile Water for Injection, USP for reconstitution

16.2 Recommended Storage

Before Reconstitution:
The GlucaGen package may be stored up to 24 months at controlled room temperature 20° to 25° C (68° to 77°F) prior to reconstitution. Do not freeze. Keep in the original package to protect from light.

After Reconstitution:
Use the reconstituted GlucaGen solution immediately. Discard any unused portion *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved (Patient Information and Instructions for Use).

Recognition of Severe Hypoglycemia

Inform patient and family members or caregivers on how to recognize the signs and symptoms of severe hypoglycemia and the risks of prolonged hypoglycemia.

Administration

Review the Patient Information and Instructions for Use with the patient and family members or caregivers.

Serious Hypersensitivity

Inform patients that allergic reactions can occur with GlucaGen. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.3)]*.

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

GlucaGen® and HypoKit® are registered trademarks of Novo Nordisk A/S

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-800-727-6500
www.novonordisk-us.com

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GlucaGen® (glucagon) for injection, for subcutaneous, intramuscular or intravenous use
Initial U.S. Approval: 1960

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2)----------03/2021
Contraindications (4)----------03/2021
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7, 5.8)----------03/2021

----------INDICATIONS AND USAGE----------
GlucaGen is an antihypoglycemic agent and a gastrointestinal motility inhibitor indicated:

- for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes (1.1)
- as a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in adult patients (1.2)

----------DOSAGE AND ADMINISTRATION----------
Dosage in adults and pediatric patients using the GlucaGen HypoKit to treat severe hypoglycemia (2.2)

- Adults and Pediatric Patients Weighing 25 kg or More or for Pediatric Patients with Unknown Weight 6 Years and Older:
  -The recommended dosage is 1 mg (1 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.
  -If there has been no response after 15 minutes, an additional 1 mg dose (1 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.
- Pediatric Patients Weighing Less Than 25 kg or for Pediatric Patients with Unknown Weight Less Than 6 Years of Age:
  -The recommended dosage is 0.5 mg (0.5 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.
  -If there has been no response after 15 minutes, an additional 0.5 mg dose (0.5 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

Important Administration Instructions for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia (2.1)

- GlucaGen is for subcutaneous, intramuscular, or intravenous injection. Administer intravenously ONLY under medical supervision.
- See the Full Prescribing Information for administration instructions

Dosage in Adults for Using GlucaGen Diagnostic Kit and GlucaGen 10-pack as a Diagnostic Aid (2.4)

- The recommended diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum, and small bowel is 0.2 mg to 0.5 mg administered intravenously or 1 mg administered intramuscularly; the recommended dose to relax the colon is 0.5 mg to 0.75 mg administered intravenously or 1 mg to 2 mg administered intramuscularly.
- See the Full Prescribing Information for administration instructions (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection (3):
Treatment of Severe Hypoglycemia:
1 mg single-dose vial of GlucaGen with a 1 mL single-dose syringe of Sterile Water for Injection, USP (GlucaGen HypoKit®)
Use as a Diagnostic Aid:
1 mg single-dose vial of GlucaGen
1 mg single-dose vial of GlucaGen with a 1 mL single-dose vial of Sterile Water for Injection, USP (Diagnostic Kit)

----------CONTRAINDICATIONS----------

- Pheochromocytoma (4)
- Insulinoma (4)
- Known hypersensitivity to glucagon or to any of the excipients (4)
- Glucagonoma when used as a diagnostic aid (4)

----------WARNINGS AND PRECAUTIONS----------
Substantial Increase in Blood Pressure in Patients with Pheochromocytoma: Contraindicated in patients with pheochromocytoma because GlucaGen 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; however, GlucaGen may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of GlucaGen, give glucose orally or intravenously. (4, 5.2)
Hypersensitivity and Allergic Reactions: Allergic reactions have been reported and include generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. (4, 5.3)
Lack of Efficacy in Patients with Decreased Hepatic Glycogen: GlucaGen 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 GlucaGen to be effective. Patients with these conditions should be treated with glucose. (5.4)
Necrolytic Migratory Erythema (NME): a skin rash, has been reported postmarketing following continuous glucagon infusion and resolved with discontinuation of the glucagon. Should NME occur, consider whether the benefits of continuous glucagon infusion outweigh the risks. (5.5)
Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid: Treatment with GlucaGen in patients with diabetes mellitus may cause hyperglycemia. Monitor diabetic patients for changes in blood glucose levels during treatment and treat if indicated. (5.6)
Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when Used as a Diagnostic Aid: GlucaGen may increase myocardial oxygen demand, blood pressure, and pulse rate. Cardiac monitoring is recommended in patients with cardiac disease during use of GlucaGen as a diagnostic aid, and an increase in blood pressure and pulse rate may require therapy. (5.7)
Hypoglycemia in Patients with Glucagonoma:
Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Test patients suspected of having glucagonoma for blood levels of glucagon prior to treatment. (5.8)

----------ADVERSE REACTIONS----------

Glucagon adverse reactions identified during post approval use are: injection site reactions, nausea, vomiting, headache, dizziness, asthenia, pallor, diarrhea, somnolence, and decreased blood pressure.(6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or 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. (7.1)
Indomethacin: In patients taking indomethacin GlucaGen may lose its ability to raise glucose or may produce hypoglycemia. (7.2)
Anticholinergic drugs: Concomitant use of anticholinergic drugs with GlucaGen for use as a diagnostic aid is not recommended. (7.3)
Warfarin: GlucaGen may increase the anticoagulant effect of warfarin. (7.4)
Insulin: Monitor blood glucose when GlucaGen is used as a diagnostic aid in patients receiving insulin. (7.5)

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

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Severe Hypoglycemia

GlucaGen is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes.

1.2 Diagnostic Aid

GlucaGen is indicated as a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia

GlucaGen is for subcutaneous, intramuscular, or intravenous injection. Administer intravenously ONLY under medical supervision.

Instruct patients and their caregivers on the signs and symptoms of severe hypoglycemia. Because severe hypoglycemia requires the help of others to recover, instruct the patient to inform those around them about GlucaGen and its Instructions for Use. Administer GlucaGen as soon as possible when severe hypoglycemia is recognized.
Instruct the patient or caregiver to read the Instructions for Use at the time they receive a prescription for GlucaGen. Emphasize the following instructions to the patient or caregiver:

- Using the supplied prefilled syringe, carefully insert the needle through the rubber stopper of the vial containing GlucaGen powder and inject all the liquid from the syringe into the vial.
- Shake the vial gently until the powder is completely dissolved and no particles remain in the fluid. The reconstituted solution should be clear and colorless. Inspect visually for particulate matter and discoloration. If the resulting solution is cloudy or contains particulate matter do not use.
- The reconstituted solution is 1 mg per mL glucagon.
- Immediately after reconstitution, using the same syringe, withdraw the correct dose of GlucaGen.
- Inject the solution subcutaneously or intramuscularly in the upper arm, thigh, or buttocks. In addition, healthcare providers may administer intravenously.
- Call for emergency assistance immediately after administering the dose.
- If there has been no response after 15 minutes, an additional dose of GlucaGen may be administered while waiting for emergency assistance.
- When the patient has responded to the treatment and is able to swallow, give oral carbohydrates to restore the liver glycogen and prevent recurrence of hypoglycemia.
- Discard any unused portion.

2.2 Dosage in Adults and Pediatric Patients for Using the GlucaGen HypoKit to Treat Severe Hypoglycemia

<u>Adults and Pediatric Patients Weighing 25 kg or More or for Pediatric Patients with Unknown Weight 6 Years and Older</u>

- The recommended dosage is 1 mg (1 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.

- If there has been no response after 15 minutes, an additional 1 mg dose (1 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

Pediatric Patients Weighing Less Than 25 kg or for Pediatric Patients with Unknown Weight Less Than 6 Years of Age

- The recommended dosage is 0.5 mg (0.5 mL) injected subcutaneously or intramuscularly into the upper arm, thigh, or buttocks, or intravenously.

- If there has been no response after 15 minutes, an additional 0.5 mg dose (0.5 mL) of GlucaGen may be administered using a new kit while waiting for emergency assistance.

For GlucaGen Diagnostic Kit and the GlucaGen 10-pack:

2.3 Important Administration Instruction for Using GlucaGen Diagnostic Kit and the GlucaGen 10-pack as a Diagnostic Aid

- Reconstitute GlucaGen with 1 mL of Sterile Water for Injection. Using a syringe, withdraw all of the Sterile Water for Injection (if supplied) or 1 mL Sterile Water for Injection and inject into the GlucaGen vial.

- Shake the vial gently until the powder is completely dissolved and no particles remain in the fluid. The reconstituted fluid should be clear and colorless. Inspect visually for particulate matter and discoloration. If the resulting solution is cloudy or contains particulate matter do not use.

- The reconstituted solution is 1 mg per mL glucagon.

- Immediately after reconstitution, inject the solution intravenously or intramuscularly into upper arm, thigh, or buttocks.

- Discard any unused portion.

- After the end of the diagnostic procedure, give oral carbohydrates to patients who have been fasting, if this is compatible with the diagnostic procedure.

2.4 Dosage in Adults for Using GlucaGen Diagnostic Kit and GlucaGen for Injection Single-Dose Vial as a Diagnostic Aid

- The recommended diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum, and small bowel is 0.2 mg to 0.5 mg administered intravenously or 1 mg administered intramuscularly; the recommended dose to relax the colon is 0.5 mg to 0.75 mg administered intravenously or 1 mg to 2 mg administered intramuscularly *[see Clinical Pharmacology (12.2)]*.

- The onset of action after an injection will depend on the organ under examination and route of administration *[see Clinical Pharmacology (12.2)]*.

3 DOSAGE FORMS AND STRENGTHS

GlucaGen for injection is a white lyophilized powder supplied as follows:

Treatment of Severe Hypoglycemia

- 1 mg single-dose vial of GlucaGen with a 1 mL single-dose syringe of Sterile Water for Injection, USP (GlucaGen HypoKit®)

Use as a Diagnostic Aid

- 1 mg single-dose vial of GlucaGen
- 1 mg single-dose vial of GlucaGen with a 1 mL single-dose vial of Sterile Water for Injection, USP (Diagnostic Kit)

4 CONTRAINDICATIONS

GlucaGen is contraindicated in patients with:

- Pheochromocytoma because of the risk of substantial increase in blood pressure [*see Warnings and Precautions (5.1)*]
- Insulinoma because of the risk of hypoglycemia [*see Warnings and Precautions (5.2)*]
- Known hypersensitivity to glucagon or the excipients in GlucaGen. Allergic reactions have been reported with glucagon and include anaphylactic shock with breathing difficulties and hypotension *[see Warnings and Precautions (5.3)]*
- Glucagonoma when used as a diagnostic aid because of risk of hypoglycemia *[see Warnings and Precautions (5.8)]*

5 WARNINGS AND PRECAUTIONS

5.1 Substantial Increase in Blood Pressure in Patients with Pheochromocytoma

GlucaGen is contraindicated in patients with pheochromocytoma because GlucaGen may stimulate the release of catecholamines from the tumor *[see Contraindications (4)]*. If the patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure for the short time that control would be needed.

5.2 Hypoglycemia in Patients with Insulinoma

In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, GlucaGen administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. GlucaGen is contraindicated in patients with insulinoma *[see Contraindications (4)]*. If a patient develops symptoms of hypoglycemia after a dose of GlucaGen, give glucose orally or intravenously.

5.3 Hypersensitivity and Allergic Reactions

Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. GlucaGen is contraindicated in patients with a prior hypersensitivity reaction *[see Contraindications (4)]*.

5.4 Lack of Efficacy in Patients with Decreased Hepatic Glycogen

GlucaGen 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 GlucaGen administration to be effective. Patients with these conditions should be treated with glucose.

5.5 Necrolytic Migratory Erythema

Necrolytic migratory erythema (NME), a skin rash commonly associated with glucagonomas (glucagon-producing tumors) and characterized by scaly, pruritic erythematous plaques, bullae, and erosions, has been reported postmarketing following continuous glucagon infusion. NME lesions may affect the face, groin, perineum and legs or be more widespread. In the reported cases NME resolved with discontinuation of the glucagon, and treatment with corticosteroids was not effective. Should NME occur, consider whether the benefits of continuous glucagon infusion outweigh the risks.

5.6 Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid

Treatment with GlucaGen in patients with diabetes mellitus may cause hyperglycemia. Monitor diabetic patients for changes in blood glucose levels during treatment and treat if indicated.

5.7 Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when used as a Diagnostic Aid

GlucaGen may increase myocardial oxygen demand, blood pressure, and pulse rate which may be life-threatening in patients with cardiac disease. Cardiac monitoring is recommended in patients with cardiac disease during use of GlucaGen as a diagnostic aid, and an increase in blood pressure and pulse rate may require therapy.

5.8 Hypoglycemia in Patients with Glucagonoma

Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Test patients suspected of having glucagonoma for blood levels of glucagon prior to use as a diagnostic aid as GlucaGen is contraindicated in this setting *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity and Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Necrolytic Migratory Erythema *[see Warnings and Precautions (5.5)]*
- Hyperglycemia in Patients with Diabetes Mellitus when Used as a Diagnostic Aid *[see Warnings and Precautions (5.6)]*
- Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease when Used as a Diagnostic Aid *[see Warnings and Precautions (5.7)]*

The following adverse reactions have been identified during post-approval use of glucagon. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Injection site reactions
- Nausea
- Vomiting
- Headache
- Dizziness
- Asthenia
- Pallor
- Diarrhea
- Somnolence
- Generalized allergic reactions including anaphylactic shock with breathing difficulties and hypotension

- Hypertension and tachycardia
- Decreased blood pressure. Hypotension has been reported up to 2 hours after administration in patients receiving GlucaGen as premedication for upper gastrointestinal endoscopy procedures.
- Hypoglycemia and hypoglycemic coma. Patients taking indomethacin may be more likely to experience hypoglycemia following glucagon administration *[see Drug Interactions (7)]*.
- Necrolytic Migratory Erythema (NME) cases have been reported post marketing in patients receiving continuous infusion of glucagon.

7 DRUG INTERACTIONS

Table 1: Clinically Significant Drug Interactions with GlucaGen

Beta-Blockers	
Clinical Impact:	Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given GlucaGen.
Intervention:	The increase in blood pressure and heart rate may require therapy in patients with coronary artery disease.
Indomethacin	
Clinical Impact:	In patients taking indomethacin, GlucaGen may lose its ability to raise blood glucose or may even produce hypoglycemia.
Intervention:	Monitor blood glucose levels during GlucaGen treatment of patients taking indomethacin.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs and GlucaGen increase the risk of gastrointestinal adverse reactions due to additive effects on inhibition of gastrointestinal motility.
Intervention:	Concomintant use of anticholinergic drugs with GlucaGen for use as a diagnostic aid is not recommended.
Warfarin	
Clinical Impact:	GlucaGen may increase the anticoagulant effect of warfarin.
Intervention:	Monitor patients for unusual bruising or bleeding, as adjustments in warfarin dosage may be required.
Insulin	
Clinical Impact:	Insulin acts antagonistically to glucagon.
Intervention:	Monitor blood glucose when GlucaGen is used as a diagnostic aid in patients receiving insulin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Multiple small studies have

demonstrated a lack of transfer of pancreatic glucagon across the human placental barrier during early gestation. In rat and rabbit reproduction studies, no embryofetal toxicity was observed with glucagon administered by injection during the period of organogenesis at doses representing up to 100 and 200 times the human dose, respectively, based on body surface area (mg/m^2) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In rats and rabbits given glucagon by injection at doses of 0.4, 2, and 10 mg/kg (up to 100 and 200 times the human dose based on mg/m^2 for rats and rabbits, respectively) there was no evidence of increased malformations or embryofetal lethality.

8.2 Lactation

Risk Summary

There is no information available on the presence of glucagon in human or animal milk, the effects of glucagon on the breastfed child or the effects of glucagon on milk production. However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore, unlikely to cause harm to an exposed infant.

8.4 Pediatric Use

The safety and effectiveness of GlucaGen for the treatment of severe hypoglycemia in pediatric patients with diabetes have been established.

Safety and effectiveness for use as a diagnosic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in pediatric patients have not been established.

10 OVERDOSAGE

If overdosage occurs, the patient may experience nausea, vomiting, inhibition of gastrointestinal tract motility, increase in blood pressure and pulse rate. In case of suspected overdosing, the serum potassium may decrease and should be monitored and corrected if needed. If the patient develops a dramatic increase in blood pressure, phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

11 DESCRIPTION

Glucagon is an antihypoglycemic agent and a gastrointestinal motility inhibitor. It is produced by expression of recombinant DNA in a *Saccharomyces cerevisiae* vector with subsequent purification. The chemical structure of the glucagon is identical to human glucagon. Glucagon with the empirical formula of $C_{153}H_{225}N_{43}O_{49}S$, and a molecular weight of 3483, is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-
1 2 3 4 5 6 7 8 9 10 11

Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-
12 13 14 15 16 17 18 19 20 21 22

Val-Gln-Trp-Leu-Met-Asn-Thr
23 24 25 26 27 28 29

GlucaGen is a sterile, lyophilized white powder for reconstitution for subcutaneous, intramuscular or intravenous use, supplied in a 2 mL vial (appearance of the powder may vary, and occasionally the powder may appear compacted). Each vial for reconstitution contains 1 mg of glucagon, 107 mg of lactose monohydrate, hydrochloric acid and sodium hydroxide. Hydrochloric acid and/or sodium hydroxide may be used to adjust the pH before lyophilization. The reconstituted solution of GlucaGen contains glucagon 1 mg/mL at pH 2.5-3.5, and is soluble in water.

12 CLINICAL PHARMACOLOGY

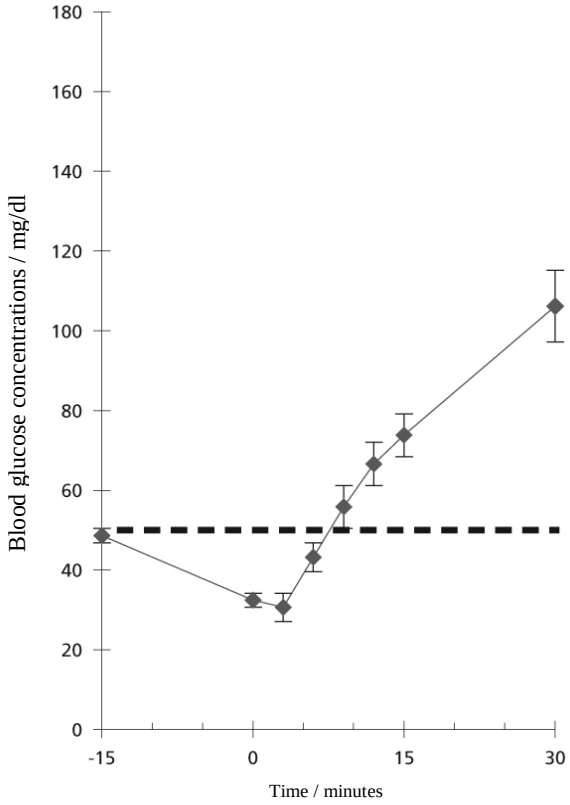
12.1 Mechanism of Action

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect. Extrahepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon.

12.2 Pharmacodynamics

Treatment of Severe Hypoglycemia:
Blood glucose concentration rises within 10 minutes of injection and maximal concentrations are attained at approximately 30 minutes after injection (see Figure 1). The duration of hyperglycemic action after intravenous or intramuscular injection is 60-90 minutes.

Figure 1. Recovery from Insulin Induced Hypoglycemia (mean blood glucose) after Intramuscular Injection of 1 mg GlucaGen in Type 1 Diabetic Men



Diagnostic Aid:

Table 2: Pharmacodynamic Properties of Glucagon for Intravenous Route

Route of Administration	Dose[a]	Time of Maximal Glucose Concentration	Time of Onset of Action for GI Smooth Muscle Relaxation	Duration of Smooth Muscle Relaxation
Intravenous	0.25 to 0.5 mg	5 to 20 minutes	45 seconds	9 to 17 minutes

[a]Dose is determined based on the length of the procedure.

Table 3: Pharmacodynamic Properties of GlucaGen for Intramuscular Route

Route of Administration	Dose[a]	Time of Maximal Glucose Concentration	Time of Onset of Action for GI Smooth Muscle Relaxation	Duration of Smooth Muscle Relaxation
Intramuscular	1 mg	30 minutes	8 to 10 minutes	12 to 27 minutes
	2 mg	30 minutes	4 to 7 minutes	21 to 32 minutes

[a]Dose is determined based on the length of the procedure.

The time of maximal glucose concentration for GlucaGen administered subcutaneously is 30-45 minutes.

12.3 Pharmacokinetics

Absorption

Intramuscular injection of 1 mg GlucaGen resulted in a mean C_{max} (CV%) of 1686 pg/mL (43%) and median T_{max} of 12.5 minutes.

Elimination

The mean apparent half-life of 45 minutes after intramuscular injection probably reflects prolonged absorption from the injection site.

Metabolism

Glucagon is degraded in the liver, kidney, and plasma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals to evaluate carcinogenic potential have not been performed.

Mutagenesis

The mutagenic potential tested in the Ames and human lymphocyte assays, was borderline positive under certain conditions for both glucagon (pancreatic) and glucagon (rDNA) origin. Doses of 100 and 200 mg/kg of glucagon of both pancreatic and recombinant origins gave slightly higher incidences of micronucleus formation in male mice but there was no effect in females. The weight of evidence indicates that synthetic and recombinant glucagon are not different and do not pose a genotoxic risk to humans

Impairment of Fertility

Glucagon was not tested in animal fertility studies. Studies in rats have shown that pancreatic glucagon does not cause impaired fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

GlucaGen for injection is supplied as a lyophilized white powder available as follows:

Presentation	NDC	Strength	Description
Treatment of Severe Hypoglycemia			
GlucaGen HypoKit	0169-7065-15	1 mg per vial	1 mL single-dose vial of GlucaGen with 1 mL single-dose syringe of

			Sterile Water for Injection, USP for reconstitution
Use as a Diagnostic Aid			
GlucaGen 10-pack: 10 Single-dose vials	0597-0053-45	1 mg per vial	1 mL single-dose vial of GlucaGen
GlucaGen Diagnostic Kit	0597-0260-10	1 mg per vial	1 mL single-dose vial of GlucaGen with 1 mL single-dose vial of Sterile Water for Injection, USP for reconstitution

16.2 Recommended Storage

Before Reconstitution:
The GlucaGen package may be stored up to 24 months at controlled room temperature 20° to 25° C (68° to 77°F) prior to reconstitution. Do not freeze. Keep in the original package to protect from light.

After Reconstitution:
Use the reconstituted GlucaGen solution immediately. Discard any unused portion *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved (Patient Information and Instructions for Use).

Recognition of Severe Hypoglycemia

Inform patient and family members or caregivers on how to recognize the signs and symptoms of severe hypoglycemia and the risks of prolonged hypoglycemia.

Administration

Review the Patient Information and Instructions for Use with the patient and family members or caregivers.

Serious Hypersensitivity

Inform patients that allergic reactions can occur with GlucaGen. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.3)]*.

Manufactured for:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

By:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

For information contact:
Boehringer Ingleheim Pharmaceuticals, Inc.
Ridgefield, CT 06877
1-800-243-0127

PATIENT INFORMATION
GlucaGen® (Glū-ka-Gen)
(glucagon)
injection,
for subcutaneous, intramuscular, or intravenous use

What is GlucaGen?
GlucaGen is a prescription medicine used:
- to treat very low blood sugar (severe hypoglycemia) in people with diabetes.
- as diagnostic aid during certain radiologic tests to temporarily stop stomach movement in adults.

It is not known if GlucaGen is safe and effective for use in children, to temporarily stop stomach movement during radiologic tests.

Who should not use GlucaGen?
Do not use GlucaGen if:
- you have a tumor in the gland on top of your kidneys (adrenal gland) called a pheochromocytoma.
- you have a tumor in your pancreas called an insulinoma.
- you are allergic to glucagon or any of the ingredients in GlucaGen. See the end of this Patient Information leaflet for a complete list of ingredients in GlucaGen.
- you have a tumor in your pancreas called a glucagonoma because it could cause low blood sugar when used for your radiology tests.

What should I tell my doctor before using GlucaGen?
Before using GlucaGen, tell your doctor about all of your medical conditions, including if you:
- have kidney problems.
- have adrenal gland problems (adrenal insufficiency).
- have pancreas problems. Tumors in your pancreas called insulinomas or glucagonomas.
- have not had food or water for a long time (prolonged fasting or starvation).
- have low blood sugar that does not go away (chronic hypoglycemia).
- have diabetes mellitus.
- have heart problems.
- are pregnant or plan to become pregnant. It is not known if GlucaGen will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if GlucaGen passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. GlucaGen may affect the way other medicines work, and other medicines may affect how GlucaGen works. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use GlucaGen?
- Read the detailed **Instructions for Use** that come with GlucaGen**.**
- Use GlucaGen exactly as your doctor tells you to.
- Make sure that you and your family know how to use GlucaGen the right way before you need it.
- Act quickly. Having very low blood sugar for a period of time may be harmful.
- **Call for emergency medical help right after you use GlucaGen.**
- Eat sugar or a sugar-sweetened product such as a regular soft drink or fruit juice as soon as you are able to swallow.
- Tell your doctor each time you use GlucaGen. Your doctor may need to change the dose of your diabetes medicines.

What are the possible side effects of GlucaGen?
GlucaGen may cause serious side effects, including:
- **high blood pressure**. GlucaGen can cause high blood pressure in certain people with tumors in their adrenal glands called pheochromocytoma.
- **low blood sugar**. GlucaGen can cause low blood sugar in people with tumors in their pancreas called insulinomas and glucagonomas by making too much insulin in their bodies. Signs and symptoms of low blood sugar may include:
  - sweating
  - drowsiness
  - dizziness
  - sleep disturbances
  - irregular heartbeat
  - blurred vision
  - hunger
  - slurred speech
  - restlessness
  - depressed mood
  - abnormal behavior
  - lightheadedness
  - unsteady movement
  - inability to concentrate
  - personality changes

- anxiety
- tingling in the hands, feet, lips or tongue
- headache
- tremor
- irritability

Very low blood sugar can cause passing out (loss of consciousness), confusion, seizures, and death. Talk to your doctor about how to tell if you have low blood sugar and what to do if this happens while using GlucaGen for injection. Know your symptoms of low blood sugar. Follow your doctor's instructions to treat low blood sugar.

- **serious allergic reactions.** Symptoms of a serious allergic reaction to GlucaGen may include rash, difficulty breathing, or low blood pressure (hypotension). If you have an allergic reaction, call your doctor and get emergency help right away.
- **high blood sugar**. If you receive GlucaGen before your radiology test, it can cause high blood sugar in people with diabetes mellitus. Your doctor will check your blood glucose levels during treatment with GlucaGen.
- **heart problems**. If you have heart problems and receive GlucaGen before your radiology test, you may have an increase in your blood pressure and pulse. Your doctor will monitor your heart when using GlucaGen during treatment.

The most common side effects of GlucaGen may include:

- injection site reactions
- vomiting
- dizziness
- pale skin
- feeling sleepy or drowsy
- nausea
- headache
- lack of energy
- diarrhea
- lower blood pressure

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of GlucaGen. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GlucaGen?

Before you mix the GlucaGen powder and liquid:

- Store GlucaGen at room temperature between 68°F to 77°F (20°C to 25°C) for up to 24 months (2 years).
- Check the expiration date on your vial of GlucaGen. Do not use GlucaGen if the expiration date has passed.
- Do not freeze GlucaGen.
- Keep GlucaGen in its original package and keep GlucaGen out of light.

After you mix the GlucaGen powder and liquid:

- Use GlucaGen right away.
- Throw away any unused GlucaGen.
- Do not use GlucaGen if a gel has formed, or if you see particles in the solution.

Keep GlucaGen and all medicines out of the reach of children.

General information about the safe and effective use of GlucaGen.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GlucaGen for a condition for which it was not prescribed. Do not give GlucaGen to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about GlucaGen that is written for health professionals.

What are the ingredients in GlucaGen?

Active Ingredient: glucagon.

Inactive ingredients: lactose monohydrate, hydrochloric acid, sodium hydroxide, and sterile water for reconstitution.

Manufactured by: Novo Nordisk A/S, 2880 Bagsvaerd, Denmark.

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2021

Instructions for Use
GlucaGen® (Glū-ka-Gen)
(glucagon) for injection
HypoKit®

Read this Instructions for Use before you start using GlucaGen and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor or pharmacist if you have any questions about how to use GlucaGen.

Important:
- **Read and become familiar with this Instructions for Use before an emergency happens**.
- Show your family members and others where you keep your GlucaGen HypoKit and how to use it the right way.
- Call for emergency medical help right after you use GlucaGen.
- Do not share your GlucaGen syringes or needles with another person. You may give other people a serious infection or other people may get a serious infection from you.
- The prefilled syringe that comes with your GlucaGen HypoKit is meant for use with GlucaGen only. Do not use GlucaGen syringes to inject other medicines.

How should I store GlucaGen?
Before you mix the GlucaGen powder and liquid:
- Store GlucaGen at room temperature between 68°F to 77°F (20°C to 25°C) for up to 24 months (2 years).
- Check the expiration date on your vial of GlucaGen. Do not use GlucaGen if the expiration date has passed.
- Do not freeze GlucaGen.
- Keep GlucaGen in its original package, and keep GlucaGen out of light.

After you mix the GlucaGen powder and liquid:
- Use GlucaGen right away.
- Throw away any unused GlucaGen.
- Do not use GlucaGen if a gel has formed, or if you see particles in the solution.

Supplies you will need for your GlucaGen injection (See Figure A):
- 1 GlucaGen HypoKit that contains:
  - 1 single-dose vial that contains 1 mg of GlucaGen powder (glucagon) for injection and 1 prefilled syringe with attached needle that contains 1 mL of sterile water.

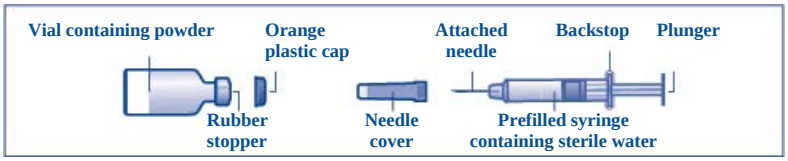


Figure A

- 1 puncture-resistant container for throwing away used needles and syringes. See “How should I dispose of (throw away) used GlucaGen prefilled syringes” at the end of these instructions.

Preparing the GlucaGen dose:

- The GlucaGen medicine comes as a dry powder. Before you use GlucaGen, you must mix the dry powder with the syringe of sterile water that comes in the GlucaGen Hypokit. **Do not use any other liquid to mix the medicine.**

- Check that the orange plastic cap on your vial of GlucaGen is firmly attached. **Do not** use the vial of GlucaGen if the orange plastic cap is loose or missing.

Step 1. Using your thumb, flip the orange plastic cap off the GlucaGen vial (**See Figure B**).

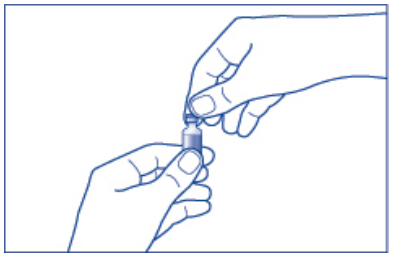


Figure B

Step 2. Pick up the prefilled syringe containing sterile water. Hold the syringe with 1 hand and with your other hand, pull the needle cover off the syringe (**See Figure C**).

- **Do not** remove the plastic backstop from the syringe.

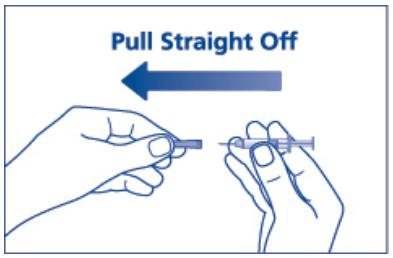


Figure C

Step 3. Pick up the GlucaGen vial. Hold the vial of dry powder with 1 hand and with your other hand, push the needle of the prefilled syringe through the center of the rubber stopper (**See Figure D**).

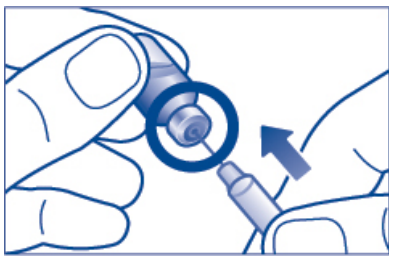


Figure D

Step 4. Hold the vial and syringe together, with the needle still inserted into the vial. Carefully turn the vial and syringe together right side up. Slowly push the plunger down until the syringe is empty (**See Figure E**).

- **Do not take the syringe out of the vial.**

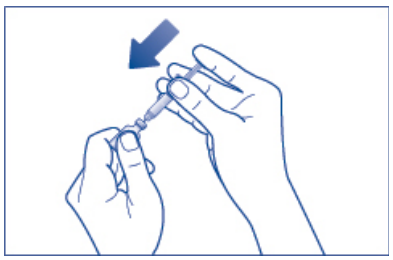


Figure E

Step 5. Hold the entire unit (the vial and syringe) in one hand and gently shake the vial until the powder is completely dissolved (**See Figure F**).

- Do not use if a gel has formed, or if you see particles in the solution.
- **Do not take the syringe out of the vial.**

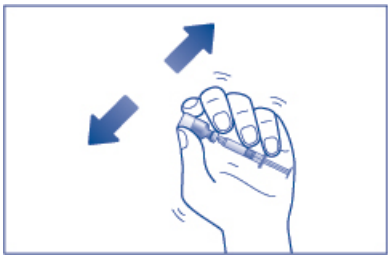


Figure F

Step 6. Firmly hold the vial and syringe together, with the needle still inserted into the vial. Carefully turn the vial and syringe together upside down. Gently pull down on the plunger and slowly withdraw all of the liquid into the syringe (**See Figure G**).

- Do not pull the plunger out of the syringe.

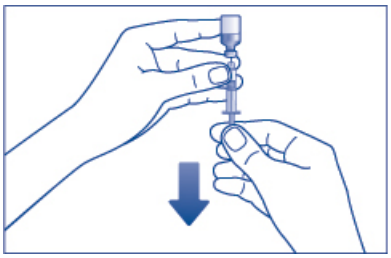


Figure G

Step 7. Keep the needle inside the vial. Check the syringe for air bubbles. If you see bubbles, tap the syringe until the bubbles rise to the top of the syringe (**See Figure H**). Gently push on the plunger to move only the air bubbles back into the vial.

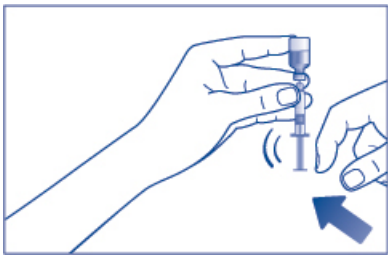


Figure H

Step 8. Hold the vial and syringe as shown (**See Figure I**).

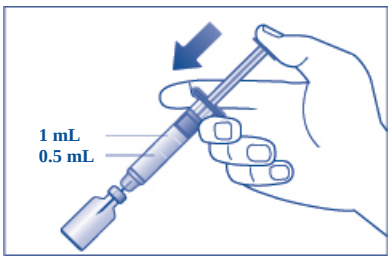


Figure I

- The usual dose for adults and children who weigh more than 55 pounds (25 kg) is 1 mg (1 mL). Use the content of the full syringe (1 mL).

- The usual dose for children who weigh less than 55 pounds (25 kg) is 0.5 mg (0.5 mL). Gently push the plunger until it is at the 0.5 mL mark on the syringe to make sure there is 0.5 mL liquid left in the syringe.

Take the syringe and needle out of the vial when the correct dose of GlucaGen is in the syringe.

If you do not know how much the child weighs:

- Give a child under 6 years of age 0.5 mg (0.5 mL).
- Give a child 6 years of age and older 1 mg (1 mL).

Giving the GlucaGen injection:

Step 9. Choose the injection site **(See Figure J**).
Common injection sites for GlucaGen are upper arms, thighs, or buttocks.

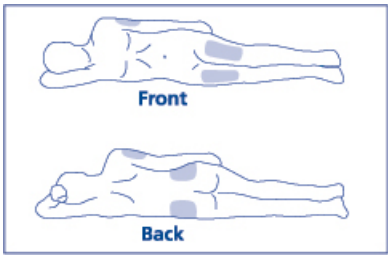


Figure J

Step 10. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into the skin and push the syringe plunger down until the syringe is empty (**See Figure K**).

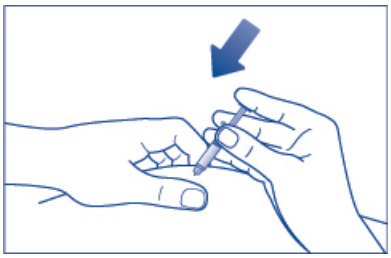


Figure K

After Giving the GlucaGen injection:

Step 11. Pull the needle out of the skin and press on the injection site (**See Figure L**).

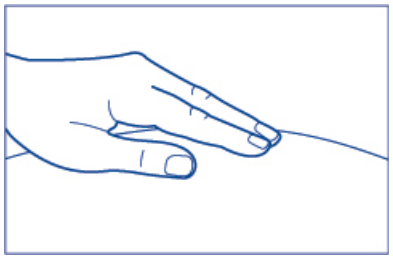


Figure L

Throw away your used syringe with the needle attached and any GlucaGen you did not use. See "**How should I dispose of (throw away) used GlucaGen prefilled syringes**" at the end of these instructions.

Step 12. Turn the person on their side. When an unconscious person awakens, they may vomit. Turning the person on their side will lessen the chance of choking.

Step 13. Call for emergency medical help right away.

Step 14. **Feed the person as soon as they are awake and able to swallow**.
Give the person a fast-acting source of sugar (such as a regular soft drink or fruit juice) and a long-acting source of sugar (such as crackers and cheese or a meat sandwich).

Step 15. If the patient does not awaken within 15 minutes, give another dose of GlucaGen. Call your doctor and get emergency help right away.

Step 16. **Even if the GlucaGen treatment wakes the person, tell their doctor right away.** The doctor should be told whenever a severe drop in blood sugar (hypoglycemia reaction) happens. The person's dose of diabetes medicine may need to be changed.

Hypoglycemia may happen again after receiving GlucaGen treatment.

Early symptoms of hypoglycemia may include:

- sweating
- drowsiness
- dizziness
- sleep disturbances
- irregular heartbeat (palpitation)
- anxiety
- tremor
- blurred vision
- hunger
- slurred speech
- restlessness
- depressed mood
- tingling in the hands, feet, lips, or tongue
- irritability
- abnormal behavior
- lightheadedness
- unsteady movement
- inability to concentrate
- personality changes
- headache

If not treated early, hypoglycemia may worsen and the person may have severe hypoglycemia. Signs of severe hypoglycemia include:

- confusion
- unconsciousness
- seizures
- death

How should I dispose of (throw away) GlucaGen pre-filled syringes?

- Put used syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Keep GlucaGen and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

GlucaGen® and HypoKit® are registered trademarks of Novo Nordisk A/S

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500
www.novonordisk-us.com

Revised: 03/2021