

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **GLUCAGON FOR INJECTION** safely and effectively. See full prescribing information for **GLUCAGON FOR INJECTION**.

### GLUCAGON for injection, for subcutaneous, intramuscular or intravenous use

Initial U.S. Approval: 1960

#### RECENT MAJOR CHANGES

Indications and Usage (1)	09/2019
Dosage and Administration (2)	09/2019
Contraindications (4)	09/2019
Warnings and Precautions (5)	09/2019

#### INDICATIONS AND USAGE

Glucagon for Injection 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 glucagon emergency kit for low blood sugar to treat severe hypoglycemia (2.2)

- Adults and Pediatric Patients Weighing More Than 25 kg 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 Glucagon for Injection 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 Glucagon for Injection may be administered using a new kit while waiting for emergency assistance.

Important Administration Instructions for Using the Glucagon Emergency Kit for Low Blood Sugar to Treat Severe Hypoglycemia (2.1)

- Glucagon for Injection 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 Glucagon for Injection Diagnostic Kit and Glucagon for Injection Single-Dose Vial 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 Glucagon for Injection with a 1 mL single-dose syringe of Sterile Water for Injection, USP (Glucagon Emergency Kit for Low Blood Sugar)
- Use as a Diagnostic Aid: 1 mg single-dose vial of Glucagon for Injection
- Use as a Diagnostic Aid: 1 mg single-dose vial of Glucagon for Injection 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

- *Catecholamine Release in Patients with Pheochromocytoma*: Contraindicated in patients with pheochromocytoma because Glucagon for Injection 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, Glucagon for Injection may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of Glucagon for Injection, 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*: Glucagon for Injection 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 Glucagon for Injection 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 Glucagon for Injection 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*: Glucagon for Injection may increase myocardial oxygen demand, blood pressure, and pulse rate. Cardiac monitoring is recommended in patients with cardiac disease during use of Glucagon for Injection as a diagnostic aid, and an increase in blood pressure and pulse rate may require therapy. (5.7)
- *Hypoglycemia in Patients with Glucagonoma when Used as a Diagnostic Aid*: Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Test patients suspected of having glucagonoma for blood levels of glucagon prior to treatment, and monitor blood glucose levels during treatment. If a patient develops hypoglycemia, give glucose orally or intravenously. (5.8)

#### ADVERSE REACTIONS

Most common adverse reactions (>5% or greater incidence): Injection site swelling, injection site erythema, vomiting, nausea, decreased blood pressure, asthenia, headache, dizziness, pallor, diarrhea, and somnolence.

**To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 Glucagon for Injection may lose its ability to raise glucose or may produce hypoglycemia. (7.2)
- *Anticholinergic drugs*: Concomitant use of anticholinergic drugs with Glucagon for Injection for use as a diagnostic aid is not recommended. (7.3)
- *Warfarin*: Glucagon for Injection may increase the anticoagulant effect of warfarin. (7.4)
- *Insulin*: Monitor blood glucose when Glucagon for Injection is used as a diagnostic aid in patients receiving insulin. (7.5)

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

Revised: 9/2019

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Severe Hypoglycemia

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

#### 1.2 Diagnostic Aid

Glucagon for Injection 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 Glucagon Emergency Kit for Low Blood Sugar to Treat Severe Hypoglycemia

Glucagon for Injection 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 Glucagon for Injection and its Instructions for Use. Administer Glucagon for Injection 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 Glucagon for Injection. 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 Glucagon for Injection 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, 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.

- 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 Glucagon Emergency Kit for Low Blood Sugar to Treat Severe Hypoglycemia**

### Adults and Pediatric Patients Weighing More Than 25 kg 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 Glucagon for Injection 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 Glucagon for Injection may be administered using a new kit while waiting for emergency assistance.

## **2.3 Important Administration Instruction for Using Glucagon for Injection Diagnostic Kit and Glucagon for Injection Single-Dose Vial as a Diagnostic Aid**

- Reconstitute Glucagon for Injection 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 Glucagon for Injection 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 Glucagon for Injection Diagnostic Kit and Glucagon 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**

Glucagon for Injection is a white lyophilized powder supplied as follows:

### Treatment of Severe Hypoglycemia

- 1 mg single-dose vial of Glucagon for Injection with a 1 mL single-dose syringe of Sterile Water for Injection, USP (Glucagon Emergency Kit for Low Blood Sugar)

### Use as a Diagnostic Aid

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

## **4 CONTRAINDICATIONS**

Glucagon for Injection is contraindicated in patients with:

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

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Catecholamine Release in Patients with Pheochromocytoma**

Glucagon for Injection is contraindicated in patients with pheochromocytoma because glucagon may stimulate the release of catecholamines from the tumor [*see Contraindications (4)*]. If the patient develops a dramatic 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.

### **5.2 Hypoglycemia in Patients with Insulinoma**

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

### **5.4 Lack of Efficacy in Patients with Decreased Hepatic Glycogen**

Glucagon for Injection 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 Glucagon for Injection 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 Glucagon for Injection 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**

Glucagon for Injection 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 Glucagon for Injection 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. Glucagon for Injection is contraindicated in patients with glucagonoma when used as a diagnostic aid [*see Contraindications (4)*]. Test patients suspected of having glucagonoma for blood levels of glucagon prior to treatment, and monitor for changes in blood glucose levels during treatment. If a patient develops symptoms of hypoglycemia after a dose of Glucagon for Injection, give glucose orally or intravenously.

### **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)*]

## 6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in clinical trials of another drug and may not reflect the rates observed in practice.

In a randomized single-blind clinical study of Glucagon for Injection, 29 healthy subjects received a single dose of 1 mg Glucagon for Injection intramuscularly. Table 1 shows the most common adverse reactions that were not present at baseline and occurred in at least 5% of patients.

**Table 1: Adverse Reactions Occurring in  $\geq 5\%$  of Healthy Subjects Who Received Glucagon for Injection Intramuscularly**

	Glucagon for Injection (N=29) % of Patients
Nausea	17
Vomiting	7

In a randomized, single-blind clinical study of Glucagon for Injection, 31 healthy subjects received a single dose of 1 mg Glucagon for Injection subcutaneously. Table 2 shows the most common adverse reactions that were not present at baseline and occurred in at least 5% of patients. (2.1)].

**Table 2: Adverse Reactions Occurring  $\geq 5\%$  in Healthy Subjects Who Received Glucagon for Injection Subcutaneously**

	Glucagon for Injection (N=31) % of Patients
Injection site swelling	58
Injection site erythema	55
Vomiting	36
Nausea	32
Decreased blood pressure	23
Asthenia	23
Headache	13
Dizziness	10
Pallor	10
Diarrhea	7
Somnolence	7

### Other Adverse Reactions

Hypertension and tachycardia have occurred with glucagon treatment.

## 6.2 Postmarketing Experience

Additional 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.

- 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 postmarketing in patients receiving continuous infusion of glucagon.

## 7 DRUG INTERACTIONS

### 7.1

**Table 3: Clinically Significant Drug Interactions with Glucagon for Injection**

<b>Beta-Blockers</b>	
<i>Clinical Impact:</i>	Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given Glucagon for Injection.
<i>Intervention:</i>	The increase in blood pressure and heart rate may require therapy in patients with coronary artery disease.
<b>Indomethacin</b>	
<i>Clinical Impact:</i>	In patients taking indomethacin, Glucagon for Injection may lose its ability to raise blood glucose or may even produce hypoglycemia.
<i>Intervention:</i>	Monitor blood glucose levels during glucagon treatment of patients taking indomethacin.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs and Glucagon for Injection increase the risk of gastrointestinal adverse reactions due to additive effects on inhibition of gastrointestinal motility.
<i>Intervention:</i>	Concomitant use of anticholinergic drugs with Glucagon for Injection for use as a diagnostic aid is not recommended.
<b>Warfarin</b>	
<i>Clinical Impact:</i>	Glucagon for Injection may increase the anticoagulant effect of warfarin.
<i>Intervention:</i>	Monitor patients for unusual bruising or bleeding, as adjustments in warfarin dosage may be required.
<b>Insulin</b>	
<i>Clinical Impact:</i>	Insulin acts antagonistically to glucagon.
<i>Intervention:</i>	Monitor blood glucose when Glucagon for Injection 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 ( $\text{mg}/\text{m}^2$ ) (*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, 2.0, and 10  $\text{mg}/\text{kg}$  (up to 100 and 200 times the human dose based on  $\text{mg}/\text{m}^2$  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 Glucagon for Injection for the treatment of severe hypoglycemia in pediatric patients with diabetes have been established.

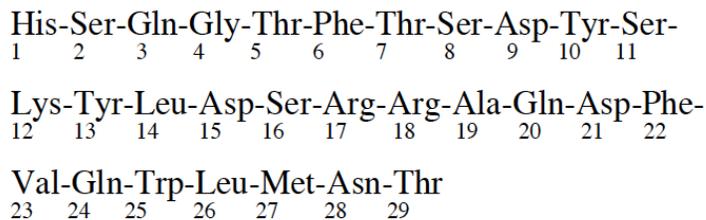
Safety and effectiveness for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in pediatric patients have not been established.

## 10 OVERDOSAGE

If overdosage occurs, the patient may experience nausea, vomiting, inhibition of GI 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 solid phase peptide synthesis. The chemical structure of the glucagon is identical to human glucagon. Glucagon is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is:



Molecular Formula =  $C_{153}H_{225}N_{43}O_{49}S$

Molecular Weight = 3483

Glucagon for Injection is a sterile, lyophilized white powder in a 3 mL vial for subcutaneous, intramuscular or intravenous use. The reconstituted solution contains glucagon as hydrochloride 1 mg per mL and lactose monohydrate (107 mg). Glucagon for Injection is supplied at pH 2.5 to 3.5 and is soluble in water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

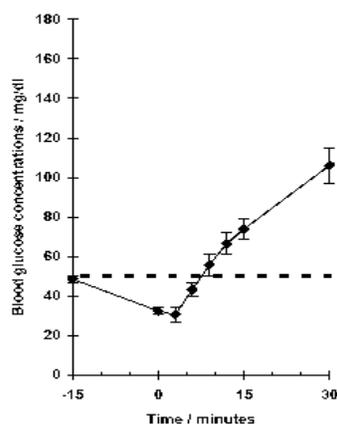
Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect. Extrahepatic effects of glucagon include 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 to 90 minutes.

**Figure 1. Recovery from Insulin Induced Hypoglycemia (mean blood glucose) After Intramuscular Injection of 1 mg of Another Glucagon for Injection Product in Type I Diabetic Men**



### Diagnostic Aid

**Table 4: Pharmacodynamic Properties of Another Glucagon for Injection Product For Intravenous Route**

Route of Administration	Dose <sup>a</sup>	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

<sup>a</sup>Dose is determined based on the length of the procedure.

**Table 5 Pharmacodynamic Properties of Another Glucagon for Injection Product For Intramuscular Route**

<b>Route of Administration</b>	<b>Dose<sup>a</sup></b>	<b>Time of Maximal Glucose Concentration</b>	<b>Time of Onset of Action for GI Smooth Muscle Relaxation</b>	<b>Duration of Smooth Muscle Relaxation</b>
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

<sup>a</sup>Dose is determined based on the length of the procedure.

In a study in healthy subjects, a subcutaneous dose of 1 mg Glucagon for Injection resulted on average a peak blood glucose concentration of 79.3 mg/dL with a median time of 50 minutes after injection.

### 12.3 Pharmacokinetics

#### Absorption

Following subcutaneous administration of Glucagon for Injection, the median time to reach the maximum baseline uncorrected plasma glucagon concentrations of 3533 pg/mL was approximately 10 to 13 minutes after dosing. Following intramuscular administration of 1 mg dose, the maximum baseline uncorrected plasma glucagon concentrations of 3391 pg/mL were attained approximately 10 minutes after dosing.

#### Elimination

The mean apparent half-life of glucagon was about 42 minutes after subcutaneous administration. The mean apparent half-life of glucagon was 26 minutes after intramuscular administration.

#### *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

Synthetic glucagon was negative in the bacterial reverse mutation assay (Ames test). The clastogenic potential of synthetic glucagon in the Chinese Hamster Ovary (CHO) assay was positive in the absence

of metabolic activation. 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**

Glucagon for Injection is supplied as a sterile, lyophilized white powder available as follows:

Presentation	NDC	Strength	Description
<b>Treatment of Severe Hypoglycemia</b>			
Glucagon Emergency Kit for Low Blood Sugar	63323-582-82	1 mg per vial	1 mL single-dose vial of Glucagon for Injection with 1 mL single-dose syringe of Sterile Water for Injection, USP for reconstitution
<b>Use as a Diagnostic Aid</b>			
10 Single-dose vials	63323-596-13	1 mg per vial	1 mL single-dose vial of Glucagon for Injection
Diagnostic Kit	63323-593-03	1 mg per vial	1 mL single-dose vial of Glucagon for Injection with 1 mL single-dose vial of Sterile Water for Injection, USP for reconstitution

**16.2 Recommended Storage**

Before Reconstitution

The package containing Glucagon for Injection vials may be stored up to 24 months at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature] prior to reconstitution. Do not freeze. Keep in the original package to protect from light.

After Reconstitution

Use reconstituted glucagon solution immediately. Discard any unused portion [see Dosage and Administration (2.3)].

**17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (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 Glucagon for Injection. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [*see Warnings and Precautions (5.3)*].