

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201849Orig1s000**

**LABELING**

## 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 intravenous or intramuscular use**  
Initial U.S. Approval: 1998

### -----INDICATIONS AND USAGE-----

Glucagon for Injection is a gastrointestinal motility inhibitor indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal (GI) tract (1)

#### Limitations of Use:

Glucagon for Injection is not indicated for the emergency treatment of hypoglycemia (1)

### -----DOSAGE AND ADMINISTRATION-----

- Reconstitute lyophilized powder with Sterile Water for Injection before use (2.2, 2.3)
- Determine dose based on diagnostic procedure, route of administration and procedure duration (2.1):
  - To inhibit stomach and small bowel motility the dose is 0.2 mg to 0.5 mg given intravenously or 1 mg given intramuscularly
  - To inhibit colon motility the dose is 0.5 mg to 0.75 mg given intravenously or 1 mg to 2 mg given intramuscularly

### -----DOSAGE FORMS AND STRENGTHS-----

For Injection: 1 mg lyophilized powder in single dose vial for reconstitution (3)

### -----CONTRAINDICATIONS-----

- Pheochromocytoma (4, 5.1)
- Insulinoma (4, 5.2)

- Glucagonoma (4, 5.2)

### -----WARNINGS AND PRECAUTIONS-----

- Hyperglycemia in patients with diabetes: Monitor blood glucose and treat with insulin if indicated (5.3)
- Increased blood pressure and heart rate in patients with cardiac disease: Monitor patients with known cardiac disease (5.4)
- Allergic reactions including anaphylactic shock with breathing difficulties, and hypotension, generalized rash: Discontinue and treat as indicated (5.5)

### -----ADVERSE REACTIONS-----

Adverse reactions seen with glucagon are transient changes in blood pressure, increase in heart rate, hypersensitivity reactions, nausea and vomiting, and hypoglycemia (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance & Medical Affairs 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: May cause a greater increase in both heart rate and blood pressure (7)
- Insulin: Reacts antagonistically towards glucagon; monitor glucose (7)
- Indomethacin: May produce hypoglycemia; monitor glucose (7)
- Anticholinergic Drugs: Concomitant use not recommended due to increased gastrointestinal adverse reactions (7)
- Warfarin: May increase anticoagulant effect of warfarin; may require an adjustment in warfarin dosage (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2015

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Glucagon for Injection is indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

#### Limitations of Use:

Glucagon for Injection is not indicated for the emergency treatment of hypoglycemia because it is not packaged with a syringe and diluent necessary for rapid preparation and administration during an emergency outside of a healthcare facility.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

Determine the dose based on the type of diagnostic procedure, the route of administration and expected procedure duration [see *Clinical Pharmacology (12.2)*].

The usual dose to inhibit movement of the:

- Stomach and small bowel is 0.2 mg to 0.5 mg given intravenously or 1 mg given intramuscularly.
- Colon is 0.5 mg to 0.75 mg given intravenously or 1 mg to 2 mg given intramuscularly.

Bolus doses above 1 mg administered intravenously have caused nausea and vomiting and are not recommended [see *Adverse Reactions (6)*].

#### 2.2 Reconstitution of the Lyophilized Powder

Glucagon for Injection is a lyophilized powder, which requires reconstitution with Sterile Water for Injection prior to intravenous or intramuscular use.

- Using a syringe, withdraw 1 mL of Sterile Water for Injection and inject into the vial containing Glucagon for Injection lyophilized powder.
- Shake the vial gently until the powder is completely dissolved and no particles remain in the reconstituted solution.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and of water-like consistency. Discard the reconstituted solution if there are signs of gel formation or particles.
- The reconstituted solution has a concentration of approximately 1 mg of glucagon per mL.
- Use the reconstituted glucagon immediately after reconstitution.

#### 2.3 Important Administration Instructions

- Glucagon for Injection must be administered by medical personnel.
- The timing of administration of Glucagon for Injection depends upon the organ under examination and route of administration [see *Clinical Pharmacology (12.2)*].
- If given intravenously, administer Glucagon for Injection as a bolus over a time period of 1 minute.
- 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.

### 3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of lyophilized powder in single dose vial for reconstitution.

### 4 CONTRAINDICATIONS

Glucagon for Injection is contraindicated in patients with:

- Pheochromocytoma [*see Warnings and Precautions (5.1)*] because of the risk of increased blood pressure
- Insulinoma [*see Warnings and Precautions (5.2)*] because of the risk of hypoglycemia
- Glucagonoma [*see Warnings and Precautions (5.2)*] because of the risk of hypoglycemia

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypertension in Patients with Pheochromocytoma

Glucagon for Injection is contraindicated in patients with pheochromocytoma because glucagon may stimulate the release of catecholamines from the tumor, which may result in a sudden and marked increase in blood pressure.

### 5.2 Hypoglycemia in Patients with Insulinoma or Glucagonoma

Glucagon for Injection is contraindicated in patients with insulinoma or glucagonoma as it may cause secondary hypoglycemia. 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, administer glucose orally or intravenously.

### 5.3 Hyperglycemia in Patients with Diabetes Mellitus

Treatment with Glucagon for Injection in patients with diabetes mellitus may cause hyperglycemia. Monitor diabetic patients for changes in blood glucose levels during treatment. If patients develop symptoms of hyperglycemia after a dose of Glucagon for Injection, administer insulin.

### 5.4 Blood Pressure and Heart Rate Increase in Patients with Cardiac Disease

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 glucagon treatment, and an increase in blood pressure and pulse rate may require therapy.

### 5.5 Hypersensitivity and Allergic Reactions

Generalized allergic reactions and hypersensitivity, including generalized rash, and anaphylactic shock with breathing difficulties, and hypotension, have been reported with glucagon treatment or lactose. Discontinue Glucagon for Injection and administer standard treatment for anaphylaxis if needed.

## 6 ADVERSE REACTIONS

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

- Hypertension in patients with Pheochromocytoma [*see Contraindications (4) and Warnings and Precautions (5.1)*]
- Hypoglycemia in Patients with Insulinoma and Glucagonoma [*see Contraindications (4) and Warnings and Precautions (5.2)*]
- Hyperglycemia in Patients with Diabetes Mellitus [*see Warnings and Precautions (5.3)*]
- Hypersensitivity and Allergic Reactions; generalized allergic reactions including generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension [*see Warnings and Precautions (5.5)*]

### Adverse Reactions from Clinical Trials

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 an open-label clinical study of Glucagon for Injection, 29 healthy volunteers 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 in Healthy Volunteers Who Received Glucagon for Injection, 1 mg Administered Intramuscularly**

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

Adverse Reactions from the Literature and Other Clinical Studies

The following adverse reactions have been identified from the literature and clinical studies with the use of glucagon. Therefore, it is not possible to reliably estimate their frequency.

- Nausea and vomiting occurred with doses above 1 mg administered by rapid intravenous injection (within 1 to 2 seconds). Doses above 1 mg are not recommended for intravenous use [see Dosage and Administration (2.1)].
- Hypotension was reported up to 2 hours after administration in patients receiving glucagon as premedication for upper GI endoscopy procedures.
- A temporary increase in both blood pressure and pulse rate occurred following the administration of glucagon. Patients taking beta-blockers experienced a temporary increase in both pulse and blood pressure that was greater than normal [see Drug Interactions (7)].
- Other adverse reactions included hypoglycemia and hypoglycemic coma, as described in postmarketing reports. Patients taking indomethacin may be more likely to experience hypoglycemia following glucagon administration [see Drug Interactions (7)].

**7 DRUG INTERACTIONS**

Table 2 includes clinically significant drug interactions with Glucagon for Injection.

**Table 2: Clinically Significant Drug Interactions with Glucagon for Injection**

<b>Beta-Blockers</b>	
<i>Clinical Impact:</i>	The concomitant use of beta-blockers and Glucagon for Injection may increase the risk of a temporary increase in heart rate and blood pressure.
<i>Intervention:</i>	The increase in blood pressure and heart rate may require therapy in patients with coronary artery disease.
<b>Insulin</b>	
<i>Clinical Impact:</i>	Insulin reacts antagonistically towards glucagon.
<i>Intervention:</i>	Monitor blood glucose when Glucagon for Injection is used as a diagnostic aid in diabetes patients.
<b>Indomethacin</b>	
<i>Clinical Impact:</i>	The concomitant use of indomethacin and Glucagon for Injection may lead to 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 is not recommended.

<b>Warfarin</b>	
<i>Clinical Impact:</i>	Glucagon 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.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### **Pregnancy Category B.**

Reproduction studies were performed in rats and rabbits with another glucagon product at doses of 0.4, 2, and 10 mg per kg. These doses represent exposures of up to 100 and 200 times the human dose based on mg/m<sup>2</sup> for rats and rabbits, respectively, and revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Glucagon does not cross the human placental barrier.

### 8.3 Nursing Mothers

It is not known whether glucagon is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when glucagon is administered to a nursing woman. No clinical studies have been performed in nursing mothers, however, glucagon is a peptide and intact glucagon is not absorbed from the GI tract. Therefore, even if the infant ingested glucagon it would be unlikely to have any effect on the infant. Additionally, glucagon has a short plasma half-life thus limiting amounts available to the child.

### 8.4 Pediatric Use

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

## 10 OVERDOSAGE

If overdosage occurs, the patient may experience nausea, vomiting, inhibition of GI tract motility, increase in blood pressure and heart rate, and decrease in serum potassium. In case of suspected overdosage, monitor and correct hypokalemia. If the patient develops a severe increase in blood pressure, phentolamine mesylate may be effective in lowering blood pressure for the short time that control would be needed.

## 11 DESCRIPTION

Glucagon for Injection, for intravenous or intramuscular use, is a gastrointestinal motility inhibitor that is produced by solid phase peptide synthesis. Glucagon is a single-chain polypeptide containing 29 amino acid residues. The chemical structure of the glucagon polypeptide is identical to human glucagon and to glucagon extracted from beef and pork pancreas. 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

**C<sub>153</sub>H<sub>225</sub>N<sub>43</sub>O<sub>49</sub>S**

**Molecular Weight = 3483**

Glucagon for Injection is a sterile, lyophilized white powder in a 3 mL vial. The reconstituted solution contains 1 mg of glucagon as hydrochloride 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

Extra hepatic effects of glucagon include relaxation of the smooth muscle of the stomach, small bowel, and colon.

### 12.2 Pharmacodynamics

Table 3 displays the pharmacodynamics properties of Glucagon for Injection as a diagnostic aid during radiologic examination.

**Table 3: Pharmacodynamic Properties of Glucagon for Injection as a Diagnostic Aid**

Route of Administration	Dose <sup>a</sup>	Time of Onset of Action for GI Smooth Muscle Relaxation	Duration of Smooth Muscle Relaxation
Intravenous	0.25 to 0.5 mg	45 seconds	9 to 17 minutes
Intramuscular	1 mg	8 to 10 minutes	12 to 27 minutes
	2 mg	4 to 7 minutes	21 to 32 minutes

<sup>a</sup>Select from these doses based on type of diagnostic procedure, route of administration and procedure duration..

### 12.3 Pharmacokinetics

#### Absorption

Following intramuscular administration of 1 mg dose, the maximum plasma glucagon concentrations of 3391 pg/mL were attained approximately 10 minutes after dosing.

#### Metabolism

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

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 (rDNA and synthetic origin) 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 in a vial.

**Product #**

**NDC #**

The container closure is not made with natural rubber latex.

## 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

The Glucagon for Injection must be reconstituted with Sterile Water for Injection prior to use. Use reconstituted glucagon solution immediately. Discard any unused portion [see *Dosage and Administration* (2.3)].

## 17 PATIENT COUNSELING INFORMATION

- Inform patients that generalized allergic reactions have been reported with glucagon treatment including generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. Advise patients to monitor and report any signs or symptoms of a hypersensitivity reaction [see *Warnings and Precautions* (5.6)].
- Inform patients that hypoglycemia has occurred with treatment with glucagon. Inform patients of the symptoms of hypoglycemia and how to treat it. Advise patients to avoid driving or operating machinery until ingesting a meal. Advise patients to inform their health care provider if hypoglycemia occurs so that treatment may be given if necessary [see *Adverse Reactions* (6)].
- Inform patients with diabetes mellitus that treatment with Glucagon for Injection may increase their risk of hyperglycemia [see *Warnings and Precautions* (5.3)].
- Inform patients with cardiac disease that treatment with Glucagon for Injection may increase their risk of a transient increase in blood pressure and heart rate [see *Warnings and Precautions* (5.4)].



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**Glucagon  
for Injection**

**1 mg per vial**

For intramuscular or  
intravenous injection only.  
For diagnostic use only.

**10 Vials**

Rx only

**TO BE SOLD ONLY AS AN UNBROKEN PACKAGE**  
Glucagon as hydrochloride 1 mg, Lactose 107 mg,  
Hydrochloric acid and/or sodium hydroxide (to  
adjust pH).

Keep out of reach of children.

**STORAGE CONDITIONS**

20° to 25°C (68° to 77°F) [See USP Controlled  
Room Temperature]. Do Not Freeze, protect  
from light. Glucagon for Injection should be  
reconstituted with 1 mL Sterile Water for Injection,  
USP immediately before use. Do not store  
for later use. Read the enclosed insert before use.

The container closure is not made with natural  
rubber latex.

Parzenus Tech, Inc., LLC  
Lake Zurich, IL 60047

42801



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**Glucagon**  
for Injection  
**1 mg per vial**  
For intramuscular or  
intravenous injection.  
For diagnostic use only.  
Reconstitute with Sterile Water  
for Injection, USP Rx only

Glucagon is hydrolyzed to 1 mg  
per vial, USP  
Parsippany, NJ, USA 07054

402324

LOT/EXP

FPO

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEAN-MARC P GUETTIER  
05/08/2015