PRODUCT MONOGRAPH

GLUCAGON

Glucagon for Injection, rDNA origin

1 mg glucagon per vial

Sterile Lyophilized Powder and Diluent

Hyperglycemic Agent

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GLUCAGON
Glucagon for Injection, rDNA origin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product	Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Glucagon	Subcutaneous, intramuscular, or intravenous injection	Lyophilized powder/1 mg glucagon per vial	Each vial of glucagon contains 49.0 mg of lactose. The diluent syringe contains 1 mL of 1.2% glycerin. *For a complete listing see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

Adults:

For the Treatment of Hypoglycemia

GLUCAGON (glucagon for injection, rDNA origin) is indicated for emergency treatment of severe hypoglycemia in patients treated with insulin when unconsciousness precludes oral carbohydrates. Severe hypoglycemia should be treated with intravenous glucose if possible.

For Use as a Diagnostic Aid

GLUCAGON is indicated as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel, and colon when diminished intestinal motility would be advantageous.

Geriatrics (≥60 years of age):

Elderly patients on insulin or oral hypoglycemic agents can also be candidates for GLUCAGON, as they also have hypoglycemic unawareness because of the aging process.

Pediatrics (<18 years of age):

For the Treatment of Hypoglycemia

The use of GLUCAGON in pediatric patients has been reported to be safe and effective.

For Use as a Diagnostic Aid

No data is available; effectiveness has not been established in pediatric patients.

CONTRAINDICATIONS

GLUCAGON (glucagon for injection, rDNA origin) is contraindicated in patients with known hypersensitivity to it or in patients with pheochromocytoma.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

GLUCAGON (glucagon for injection, rDNA origin) should be given only if patients are unconscious or unresponsive and unable to ingest oral glucose. After intramuscular injection, the patient will normally respond within 10 minutes. If the patient does not respond within 10 minutes, intravenous glucose must be administered as soon as an IV access can be established.

Because glucagon is of little or no help in states of starvation, adrenal insufficiency, or chronic hypoglycemia, intravenous glucose should be used for treatment of hypoglycemia in those conditions.

General

GLUCAGON (glucagon for injection, rDNA origin) is helpful in treating hypoglycemia only if sufficient liver glycogen is present.

The patient with type 1 diabetes does not have as great response in blood glucose levels upon administration of glucagon as does the person with stable type 2 diabetes; therefore supplementary carbohydrate should be given as soon as possible, especially to a child or adolescent patient.

GLUCAGON (glucagon for injection, rDNA origin) should be administered cautiously to patients with a history suggestive of insulinoma, pheochromocytoma, or both.

Insulinoma:

In patients with insulinoma, intravenous administration of glucagon will produce an initial increase in blood glucose however, because of glucagon's insulin-releasing effect, it may cause the insulinoma to release its insulin and subsequently cause hypoglycemia. A patient developing symptoms of hypoglycemia after a dose of glucagon should be given glucose orally, intravenously, or by gavage, whichever is more appropriate.

Pheochromocytoma:

Exogenous glucagon also stimulates the release of catecholamines. In the presence of pheochromocytoma, glucagon can cause the tumour to release catecholamines, which results in a sudden and marked increase in blood pressure. If a patient suddenly develops a marked increase in blood pressure, 5 to 10 mg of phentolamine mesylate may be administered intravenously in an attempt to control the blood pressure.

Carcinogenesis and Mutagenesis

Because glucagon is usually given in a single dose and has a very short half-life, no studies have been done regarding carcinogenesis. In a series of mutagenesis studies, glucagon was determined not to be mutagenic.

Reproduction studies have been performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 120 times the human dose) and have revealed no evidence of impaired fertility. (See TOXICOLOGY)

Cardiovascular

In high concentrations, glucagon exerts positive inotropic and chronotropic effect and may therefore cause tachycardia and acute hypertensive reactions. (See CONTRAINDICATIONS)

Patient Education

Because GLUCAGON and any GLUCAGON kits are designed to be used in emergency situations in which a high level of stress will likely be involved, it is imperative that the injection or kits be easy to find and easy to use.

Specific instructions on the use of GLUCAGON should be given to patients at risk of hypoglycemia unawareness, including elderly. Specific directions for reconstitution and use should also be provided along with the injection and/or kits.

Sensitivity/Resistance

Generalized allergic reactions, including urticaria, respiratory distress, and hypotension, have been reported in patients who received glucagon.

Special Populations

Patients with type 2 diabetes:

When deciding on the use of glucagon for patients with type 2 diabetes, consider those with chronic diabetes on an intensive insulin regimen. Those with advanced type 2 diabetes have a comparable decline in counter-regulatory hormones to those with type 1 diabetes.

Usage in Pregnancy:

Reproduction studies have not been performed with recombinant glucagon; however studies with animal sourced glucagon have been performed in rats at doses up to 2 mg/kg b.i.d., (up to 120 times the human dose), and have revealed no evidence of harm to the fetus due to glucagon. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if oral carbohydrates cannot be administered.

Nursing Mothers:

It is not known whether this drug is excreted in human milk.

Pediatrics (<18 years if age):

For the treatment of hypoglycemia: The use of glucagon in pediatric patients has been reported to be safe and effective.

For use as a diagnostic aid: Effectiveness has not been established in pediatric patients.

Geriatrics (≥60 years if age):

Elderly patients on insulin or oral hypoglycemic agents can also be candidates for glucagon, as they also have hypoglycemic unawareness because of the aging process.

Use with alcohol:

Alcohol can suppress hepatic gluconeogenesis and chronic alcoholism can deplete liver glycogen stores. Therefore glucagon may be less effective in presence of acute or chronic alcohol ingestion.

Monitoring and Laboratory Tests

Blood glucose determinations should be obtained to follow the patient with hypoglycemia until the patient is asymptomatic.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Severe adverse reactions are very rare, although nausea, vomiting and hypokalemia may occur occasionally. Generalized allergic reactions, including urticaria, respiratory distress, and hypotension have been reported in patients who received glucagon (see WARNINGS AND PRECAUTIONS). In the event of lack of response to the administration of GLUCAGON, intravenous glucose should be administered to the patient.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events were reported in two clinical studies "H3F-LC-GFAA: *Comparison of Pharmacokinetic Parameters of Recombinant and Animal-Sourced Glucagon After IV, IM, and SC Injection"* and "H3F-MC-GFAB: *Safety and Immunogenicity of Recombinant DNA Glucagon in Comparison with Animal-Sourced Glucagon."* (See CLINICAL TRIALS)

Common Adverse Events Reported in Clinical Studies

For summary of the most common (>1% of subjects) adverse events for GFAA and GFAB, see Tables 1 and 2.

Table 1: GFAA: Treatment-Emergent Adverse Events Incidence for Patients Treated with SC animal-sourced glucagon (Treatment A), SC rGlucagon pH 2.8 (Treatment B), SC rGlucagon pH 2.0 (Treatment C), IM animal-sourced glucagon (Treatment D), IM rGlucagon pH 2.8 (Treatment E), and IM rGlucagon pH 2.0 (Treatment F).

Number of Patients Reporting Events N=29*						
Body System/ Adverse Event	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Treatment F
Nervous System						
Headache	--	1	1	1	1	--
Dizziness	3	--	1	--	1	--
Digestive System						
Nausea*	3	1	3	1	1	--
Vomiting	--	--	1	--	--	--
Skin and Appendages						
Pallor	--	--	1	--	--	--

-- No report of an adverse event for that treatment.
* N represents the number of patients enrolled and dosed in Part II of the GFAA study.

Table 2: GFAB: Treatment-Emergent Adverse Events Incidence in patients treated with rGlucagon and animal-sourced Glucagon in the GFAB study.

Percentage of Patients Reporting Event		
Body System/ Adverse Event	rGlucagon (N=50)*	Animal-Sourced Glucagon (N=25)*
Nervous System		
Headache	22	32
Confusion	2	--
Dizziness	24	28
Nervousness	2	4
Syncope	2	4
Digestive System		
Nausea	30	28
Vomiting	16	8
Dry mouth	2	--
Diarrhea	2	--
Dyspepsia	2	--
Taste Perversion	2	--
Skin and Appendages		
Pruritus	2	--
Rash	2	--
Sweating	2	4
Body as a Whole		
Asthenia	6	12
Back Pain	--	4
Abdominal Pain	2	--

Percentage of Patients Reporting Event		
Body System/ Adverse Event	rGlucagon (N=50)*	Animal-Sourced Glucagon (N=25)*
Pain	2	--
Thirst	2	4
Respiratory System		
Pharyngitis	2	--
Cardiovascular System		
Vasodilatation	6	20
Palpitation	--	8

-- No report of an adverse event for that treatment.
* N represents the number of patients that were enrolled for each treatment.

Abnormal Hematologic and Clinical Chemistry Findings

There were no abnormal hematologic and/or clinical chemistry findings considered related to GLUCAGON treatment.

Post-Market Adverse Drug Reactions

A post-market surveillance survey is presented below which includes undesirable effects that were reported spontaneously. GLUCAGON is relatively free of adverse reactions except for occasional nausea and vomiting, which may also occur with hypoglycemia. Generalized allergic reactions have also been reported (see WARNINGS AND PRECAUTIONS).

Table 3: Post-Marketing Experience

Body System	Subject Incidence	Adverse drug reaction
Gastrointestinal disorders	Very rarely <1/10,000	Nausea Vomiting
Immune system disorders	Very rarely <1/10,000	Allergic reaction (including urticaria, respiratory distress, and hypotension)

DRUG INTERACTIONS

Overview

Interactions between GLUCAGON and other drugs are not known, when used in diabetes.

Published literature has shown the following interactions:

Insulin: Reacts antagonistically towards glucagon.
Indomethacin: Glucagon may lose its ability to raise blood glucose or paradoxically may even produce hypoglycemia.

Warfarin: Glucagon may increase the anticoagulant effect of warfarin.

Alcohol induced hypoglycemia is associated with a failure of blood glucose levels to rise normally after the administration of glucagon.

Drug-Drug Interactions

Drug-drug interactions supported by animal or in-vitro studies have not been established.

Sulfonylurea: Use of glucagon in patients taking a sulfonylurea is not the generally recommended therapy. Due to the pharmacokinetics profile of sulfonylurea, they remain in the system for a long time and therefore can cause significant and prolonged hypoglycemia. IV glucose bolus followed by continuous IV infusion until the effects of the sulfonylurea are gone is the preferred treatment of severe hypoglycemia for those taking sulfonylureas.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

GLUCAGON (glucagon for injection, rDNA origin) should be reconstituted with the accompanying diluent following the detailed directions contained within the *Directions for User* package insert.

Recommended Dose and Dosage Adjustment

For the Treatment of Hypoglycemia:

The diluent is provided for use only in the preparation of GLUCAGON for intermittent parenteral injection and for no other use.

GLUCAGON should be reconstituted with the accompanying diluent following the detailed directions contained within the *Directions for the User* package insert.

GLUCAGON should be used immediately after reconstitution. **Discard any unused portion.**

Directions for Use of GLUCAGON:

1. Dissolve the lyophilized GLUCAGON in the accompanying diluent.
2. GLUGAGON should not be used at concentrations greater than 1 mg/mL (1 unit/mL).

3. GLUCAGON solutions should not be used unless they are clear and of a water-like consistency.
4. For adults and for children weighing more than 20 kg, give 1 mg (1 unit) by subcutaneous, intramuscular, or intravenous injection.
5. For children weighing less than 20 kg, give 0.5 mg (0.5 unit) or a dose equivalent to 20-30 µg/kg.
6. The patient will usually awaken within fifteen minutes. If the response is delayed, there is no contraindication to the administration of one or two additional doses of GLUCAGON; however, in view of the deleterious effects of cerebral hypoglycemia and depending on the duration and depth of coma, the use of parenteral glucose must be considered by the physician.
7. Intravenous glucose must be given if the patient fails to respond to GLUCAGON.
8. When the patient responds, give supplemental carbohydrate to restore the liver glycogen and prevent secondary hypoglycemia.

Instructions to the Family: Instructions describing the method of using this preparation are included in the literature that accompanies the patient's package. It is advisable for the patient and family members to become familiar with the technique of preparing GLUCAGON for injection before an emergency arises. Patients are instructed to use 1 mg (1 unit) for adults and, if recommended by a doctor, 1/2 the adult dose (0.5 mg [0.5 unit]) for children weighing less than 20 kg.

For Use as a Diagnostic Aid:

Dissolve the lyophilized GLUCAGON in the accompanying diluting solution. GLUCAGON should not be used at concentrations greater than 1 mg/mL (1 unit/mL).

The doses of GLUCAGON listed in the following table may be administered for relaxation of the stomach, duodenum, and small bowel, depending on the onset and duration of effect required for the examination. Since the stomach is less sensitive to the effect of glucagon, 0.5 mg (0.5 units) IV or 2 mg (2 units) IM are recommended.

For examination of the colon, it is recommended that a 2 mg (2 unit) dose be administered intramuscularly approximately 10 minutes prior to initiation of the procedure. Relaxation of the colon and reduction of discomfort to the patient will allow the radiologist to perform a more satisfactory examination.

Dose	Route of Administration	Time of Onset of Action	Approximate Duration of Effect
0.25–0.5 mg*	IV	1 minute	9–17 minutes
1 mg*	IM	8–10 minutes	12–27 minutes
2 mg*[¥]	IV	1 minute	22–25 minutes
2 mg*[¥]	IM	4–7 minutes	21–32 minutes

[¥] Administration of 2 mg (2 unit) doses produces a higher incidence of nausea and vomiting than do lower doses.

* 1 mg equals 1 unit.

Administration

For adults and for children weighing more than 20 kg, give 1 mg (1 unit) by subcutaneous, intramuscular, or intravenous injection.

For children weighing less than 20 kg, give 0.5 mg (0.5 unit) or a dose equivalent to 20–30 µg/kg.

GLUCAGON should be reconstituted with the accompanying diluent following the detailed directions contained within the Directions for the User package insert.

OVERDOSAGE

Signs and Symptoms:

GLUCAGON (glucagon for injection, rDNA origin) is generally well tolerated. If overdosage occurred, it would not be expected to cause consequential toxicity, but would be expected to be associated with nausea, vomiting, gastric hypotonicity, and diarrhea.

Intravenous administration of glucagon has been shown to have a positive inotropic and chronotropic effect. A transient increment in both blood pressure and pulse rate may occur following the administration of glucagon. Patients taking ß-blockers might be expected to have a greater increment in both pulse rate and blood pressure. This increase will be transient because of glucagon's short half-life. The increase in blood pressure and pulse rate may require therapy in patients with pheochromocytoma or coronary artery disease.

When glucagon was given in large doses to patients with cardiac disease, investigators reported a positive inotropic effect. These investigators administered glucagon in doses of 0.5 to 16 mg/hour by continuous infusion for periods of 5 to 166 hours. Total doses ranged from 25 to 996 mg, and a 21-month-old infant received approximately 8.25 mg in 165 hours. Side effects included nausea, vomiting, and decreasing serum potassium concentration. Serum potassium concentration could be maintained within normal limits with supplemental potassium.

The intravenous median lethal dose for glucagon in mice and rats is approximately 300 mg/kg and 38.6 mg/kg, respectively.

Because glucagon is a polypeptide, it would be rapidly destroyed in the gastrointestinal tract if it were to be accidentally ingested.

Treatment:

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

In view of the extremely short half-life of glucagon and its prompt destruction and excretion, the treatment of overdosage is symptomatic, primarily for nausea, vomiting, and possible hypokalemia.

If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine has been shown to be effective in lowering blood pressure for the short time that control would be needed.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of glucagon; it is extremely unlikely that one of these procedures would ever be indicated.

All of the results mentioned above have been obtained with animal sourced glucagon rather than recombinant glucagon. Since the structure of recombinant glucagon is identical to the animal sourced glucagon, the results obtained from the animal sourced glucagon studies are applicable to recombinant glucagon.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

GLUCAGON (glucagon for injection, rDNA origin) is a polypeptide hormone identical to human glucagon which is manufactured by recombinant DNA technology and has the same molecular structure as animal sourced glucagon. Glucagon causes an increase in blood glucose concentration. Glucagon acts only on liver glycogen, converting it to glucose. Parenteral administration of glucagon relaxes smooth muscle of the stomach, duodenum, small bowel, and colon.

Pharmacodynamics

In a study of 29 healthy volunteers, a subcutaneous dose of 1 mg glucagon resulted in a mean peak glucose concentration of 136 mg/dL (7.55 mmol/L), 30 minutes after injection for the 25 evaluable patients. Similarly, following intramuscular injection, the mean peak glucose level was 138 mg/dL (7.66 mmol/L), which occurred at 26 minutes after injection. No difference in glucodynamic activity between animal-sourced and rDNA glucagon was observed after subcutaneous and intramuscular injection.

Pharmacokinetics

Glucagon has been studied following intramuscular, subcutaneous, and intravenous administration in adult volunteers. Administration of the intravenous Glucagon showed dose proportionality of the pharmacokinetics between 0.25 and 2.0 mg. Calculations from a 1 mg dose showed a small volume of distribution (mean, 0.25 L/kg) and a moderate clearance (mean, 13.5 mL/min/kg). The half-life ranged from 8–18 minutes.

Maximum plasma concentrations of 7.9 ng/mL were achieved approximately 20 minutes after subcutaneous administration. With intramuscular dosing, maximum plasma concentrations of 6.9 ng/mL were attained approximately 13 minutes after dosing.

Glucagon is extensively degraded in liver, kidney, and plasma. Urinary excretion of intact glucagon has not been measured.

STORAGE AND STABILITY

Do not use past expiry date.

Before Reconstitution:

Prior to reconstitution, Vials of GLUCAGON and prefilled Hyporets of Diluting Solution may be stored at controlled room temperature, 15° to 30°C.

Reconstituted Solutions:

GLUCAGON should be reconstituted with the accompanying Diluent following the detailed directions contained within the *Directions for the User* package insert.

GLUCAGON should be used immediately after reconstitution. **Discard any unused portion.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

GLUCAGON (glucagon for injection, rDNA origin) in lyophilized form with accompanying diluting solution is available as:

GLUCAGON Kit containing:

VL7529 - Vial, GLUCAGON, 1 mg (1.0 units) glucagon for injection, rDNA origin, with 49.0 mg of lactose and HY7530 - prefilled Hyporet, Diluting Solution, 1 mL containing 1.2% glycerin.

Composition

Each vial of GLUCAGON contains 1 mg (1.0 units) of glucagon with 49.0 mg of lactose. The diluent syringe contains 1 mL of 1.2% glycerin. Hydrochloric acid has been added during manufacture to adjust the pH.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

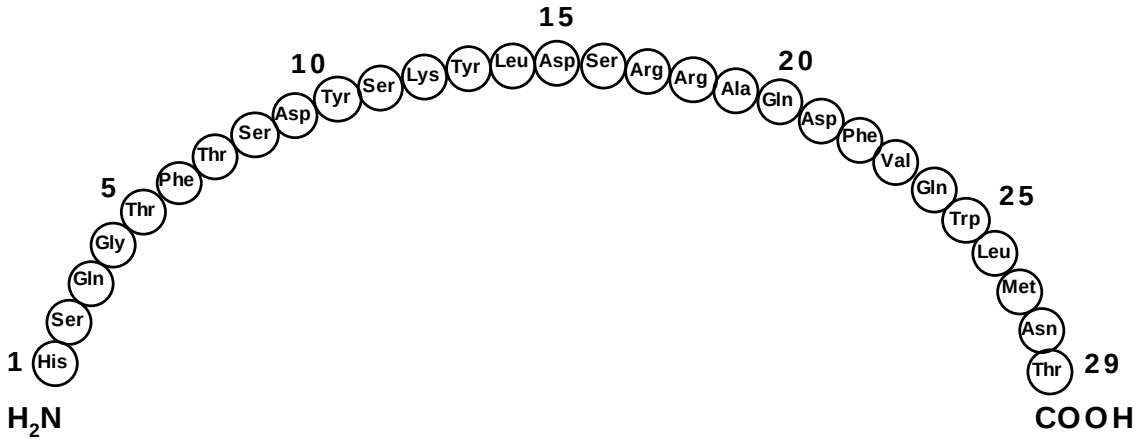
GLUCAGON (glucagon for injection, rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for glucagon.

INN/USAN Proper Name: glucagon

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

Molecular Weight: 3,483

Structure: Glucagon is a single-chain polypeptide containing 29 amino acid residues. The structure of glucagon is shown below.



Description: Crystalline glucagon is a white to off-white powder. It is relatively insoluble in water but is soluble at a pH of less than 3 or more than 9.5.

CLINICAL TRIALS

The following two pivotal clinical studies were carried out in healthy volunteers to establish clinical equivalence between rGlucagon and animal-sourced glucagon:

- H3F-LC-GFAA: *Comparison of Pharmacokinetic Parameters of Recombinant and Animal-Sourced Glucagon After IV, IM, and SC Injection.*
- H3F-MC-GFAB: *Safety and Immunogenicity of Recombinant DNA Glucagon in Comparison with Animal-Sourced Glucagon*

Study H3F-LC-GFAA was performed with the primary objective of establishing bioequivalence of recombinant bioequivalence of recombinant glucagon (rGlucagon) reconstituted with diluent at 2 separate pH values (2.0, 2.8) with existing animal-source glucagon (diluent pH 2.8) after subcutaneous (SC) and intramuscular (IM) administrations. The secondary objective of this study was to compare the safety profiles of rGlucagon and animal-source glucagon to determine the dose response, glucodynamic and pharmacokinetic behaviour of rGlucagon after intravenous administration.

Study GFAA was divided into two parts: Part I, a randomized, open label, 4-way complete block crossover intravenous dose-ranging study of rGlucagon (diluent pH 2.8), and Part II, an open label, randomized, 6-way crossover design for the assessment of bioequivalence between animal-source glucagon (diluent pH 2.8) and rGlucagon reconstituted with two separate pH values (diluent pH 2.0 and 2.8) administered subcutaneously and intramuscularly. Parts I and II were performed in a parallel fashion, with separately enrolled panels. Neither Part I nor Part II were blinded.

In Part I, 12 healthy volunteers were enrolled, and were given four separate rGlucagon doses (0.25, 0.5, 1.0, and 2.0 mg). In Part II, 29 healthy male and female volunteers participated, with a single 1 mg dose given for all 6 treatments. For both Parts I and II, blood samples were collected over a 4-hour period after injection of each treatment and assayed for immunoreactive plasma glucagon and blood glucose concentrations. All treatments were separated by a 7- to 10-day interval.

Part I (IV Dose-Ranging):

Pharmacodynamics

No statistically significant differences in glucose responses were observed among the rGlucagon doses (ranging from 0.25 to 2.0 mg), indicating that the maximum glucodynamic effect was obtained with the lowest dose administered. Mean maximal blood glucose concentrations ranged from 129 to 136 mg/dL (7.16 to 7.55 mmol/L) and occurred within 22 minutes following the IV bolus. In most subjects, blood glucose returned to baseline within 1 hour after rGlucagon injection.

Pharmacokinetics

rGlucagon (diluent pH 2.8) exhibited pharmacokinetic dose proportionality after IV administration at doses ranging from 0.25 to 2.0 mg. Plasma glucagon concentrations peaked rapidly, within 3 minutes after the IV bolus. Elimination was also swift; mean $t_{1/2}$ values ranged from 8 to 18 minutes.

Part II (SC Bioequivalence Determinations and IM Bioequivalence Determinations):

Pharmacodynamics

Comparisons of the SC treatments showed glucodynamic equivalence for maximum blood glucose concentrations and maximal absolute excursion values. rGlucagon (diluent pH 2.8) and animal-sourced glucagon showed glucodynamic equivalence for blood glucose concentration-time AUC values. rGlucagon 1 mg (diluent pH 2.0) produced the highest overall blood glucose response following SC administration.

As with the SC treatments, all IM treatments exhibited glucodynamic equivalence for blood glucose C_{max} and maximum absolute glucose excursion. Animal-sourced glucagon showed glucodynamic equivalence with both recombinant formulations, based on blood glucose AUC.

Pharmacokinetics

Pharmacokinetic comparisons of the SC administrations demonstrated that all treatments met standard bioequivalence criteria with respect to the AUC except for Cmax for plasma glucagon. The plasma glucagon Cmax value after rGlucagon (diluent pH 2.8) was slightly higher than the C_{max} value for animal-sourced glucagon, while the C_{max} for rGlucagon (diluent pH 2.0) was slightly lower.

With IM administration, both recombinant glucagon formulations were bioequivalent to animal-sourced glucagon with respect to C_{max} and glucagon AUC values.

In study GFAB the administration of 1 mg of rGlucagon (pH=2.0) resulted in comparable glucose concentration-time profiles relative to 1 mg of animal-sourced glucagon. There were no significant differences in the pharmacodynamic effects of the two glucagon sources in terms of blood glucose C_{max}, the time to reach maximum glucose concentration, AUC, maximum positive excursion, maximum negative excursion, time of maximum positive excursion, time of maximum negative excursion or AUC_{ex}. Taken together, these data indicate that rGlucagon is indistinguishable from animal-sourced glucagon in its ability to raise blood glucose after IM injection to normal volunteers.

DETAILED PHARMACOLOGY

General

The physiology and pharmacology of glucagon have been extensively characterized and thoroughly reviewed by innumerable textbooks and articles. The primary effect of this hormone is to elevate blood glucose by stimulating glycogenolysis and gluconeogenesis.

Commercial animal-source glucagon is produced through an extraction process from beef and pork pancreas glands, followed by a high degree of purification. Recombinant glucagon

(rGlucagon), on the other hand, is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by addition of the gene for glucagon. References to glucagon apply to both forms whereas references to rGlucagon only apply to recombinant glucagon for injection.

By means of hepatic vein catheterization, glucagon injections have been shown to cause a marked increase in glucose output from the liver in man. It has been demonstrated that glucagon converts liver phosphorylase from an inactive to an active state. This reaction is the rate-limiting step in the conversion of liver glycogen to glucose. Muscle phosphorylase is not affected by glucagon. Glucagon acts only on liver glycogen. The intensity of the hyperglycemic response to glucagon appears to depend upon the hepatic glycogen reserves.

The complete physiologic role of glucagon on carbohydrate metabolism has not been clearly defined. Although investigators agree that glucagon has a hepatic glycogenolytic hyperglycemic action, they are not in agreement as to whether glucagon increases the peripheral utilization of glycogen.

The specific stimulus for the secretion of glucagon from the pancreas is not known, however, experimental evidence indicates that pituitary growth hormone may stimulate glucagon secretion.

Unlike epinephrine (which also promotes an increase in active liver phosphorylase), glucagon does not produce a breakdown of muscle glycogen to lactate or pyruvate.

A glycogenolytic action of glucagon is not blocked by agents that block epinephrine. Glucagon has positive inotropic and positive chronotropic effects on isolated hearts and may cause a fall in blood pressure in anesthetized dogs and cats when given rapidly by intravenous injection.

Following the discovery that glucagon inhibited the hunger contraction, appetite, blood pepsinogen level, and basal gastric acid secretion, it was found that the meal-histamine-induced acid secretion was also significantly reduced by glucagon.

Glucagon delays gastric emptying in man and produces hypotonicity of the duodenum of healthy subjects.

Glucagon resembles cholecystokinin, gastrin, caerulein and secretin in causing bile secretion and relaxation of the choledochal sphincter, but acts opposite to these hormones on gastric and pancreatic secretion. It resembles secretin in inhibition of acid secretion and gut motility, but acts opposite to secretin in its actions upon the pancreas and the gallbladder.

In-vivo and *in-vitro* studies of cat small intestine suggest that glucagon acts directly on the smooth muscle of the intestine by a similar mechanism to beta-adrenergic agents.

Pre-clinical

The glucodynamic and pharmacokinetic effects of recombinant glucagon were investigated in CD rats and beagle dogs following daily intravenous administration for 4 weeks. Rats received doses of 0, 0.2, 1.0, or 5.0 mg of rGlucagon/kg, while dogs received doses of 0, 1.0, or 5.0 mg of rGlucagon/kg or 5.0 mg/kg of animal-sourced glucagon. Since this study was designed to assess

the toxicity of rGlucagon, the sampling time of approximately 24 hours after dosing was not optimal to define the glucodynamic response in the rats. Nevertheless, differences in blood glucose concentrations were found relative to control rats in samples collected after treatment for 4 weeks. Blood glucose concentrations were higher in male rats administered 1.0 or 5.0 mg/kg, while lower concentrations were found in female rats administered the same doses.

In dogs, no treatment effects were found, except for a change in the blood glucose concentration-time profile. At 5 minutes after dosing, glucose concentrations increased by a factor of about 2 to 3 compared to their predose levels. The glucose concentrations returned to baseline levels by about 2 hours.

A multiple-dose study of rGlucagon was conducted in beagle dogs. The dogs received daily subcutaneous doses of 0, 0.02, 0.06, or 0.2 mg rGlucagon/kg (Treatment Groups 00, 01, 02, and 03, respectively) for 2 weeks. The following conclusions were made based on pharmacodynamic and statistical analyses. First, the glucodynamic response to a subcutaneous injection of glucagon is both rapid and short-lived. In the majority of dogs the serum glucose concentrations peaked at 10 to 20 minutes following a subcutaneous injection. For male dogs, the serum glucose concentrations tended to return to baseline levels by about 1 hour. In contrast, the serum glucose concentrations persisted longer in female dogs with the dogs in Treatment Group 03 (0.20 mg rGlucagon/kg) having elevated blood glucose concentrations for at least 2 hours after subcutaneous injection of rGlucagon. Secondly, a gender difference was found between males and females with respect to AUCs and MAE, with a larger response evident in female dogs. Third, a temporal difference was found in AUC and MAE values with a greater response in both genders after daily administration for 13 days. Fourth, a dose-response was evident from single-dose data. Finally, a possible saturable response as measured by MAE may be achieved by the administration of rGlucagon.

Another study was conducted in male beagle dogs to compare the pharmacokinetics and pharmacodynamics (glucodynamics) of animal-sourced glucagon and rGlucagon, the effect of diluent pH (2.0 versus 2.8), and to determine if any repeat dose effects are present when 2 single subcutaneous doses of glucagon were administered 7 days apart. After the administration of a single 0.2 mg/kg dose of rGlucagon, systemic exposure was assessed by measuring the plasma concentrations of immunoreactive glucagon (pharmacokinetics) and the serum concentrations of glucose (pharmacodynamics). In agreement with the previous study, the pharmacodynamic responses in the dogs were quite variable in regards to AUC and MAE. Serum glucose concentrations peaked rapidly following subcutaneous administration of rGlucagon. In all treatment groups but one, the glucose concentrations reached a maximum at 0.25 hours with an overall mean of 0.27 hours. The overall mean peak glucose concentration of 180.6 mg/dL (10.03 mmol/L) was about twice the baseline concentration. The glucose concentrations returned to their baseline level by around 3 hours after dose administration. Differences in the source of glucagon (animal-sourced and recombinant) and diluent pH did not result in statistically significant differences in the glucodynamic parameters of maximum absolute glucose excursion (MAE) and AUC_{ex} values. However, an effect of repetitive dosing was found with the glucose excursion area under the curve (AUC_{ex}) parameter indicating a greater glucodynamic response on treatment Day 7 than on Day 0.

Other Pharmacological Properties of Glucagon

As listed in the table below, glucagon has been reported to possess a number of other pharmacological properties in addition to its primary effect on blood glucose. These properties may be related either directly or indirectly to the glucodynamic effect of glucagon. Based on limited experiments comparing glucodynamic effects, the other pharmacological properties of rGlucagon are expected to be equivalent to animal-sourced glucagon.

Other Pharmacological Properties of Glucagon

Property	Reference
Iontropic and chronotropic effects on heart	Farah 1983
Diuretic effect on kidney	Kolanowski 1983
Spasmolytic effect on gastrointestinal tract	Diamant and Picazo 1983
Inhibition of gastric acid secretion	Lin et al. 1973
Inhibition of hunger contraction and appetite	Stunkard et al. 1955; Penick and Hinkle 1957
Inhibition of pancreatic secretions	Dyck et al. 1970
Inhibition of ureteral motility	Boyarsky and Labay 1969
Stimulate hepatic release of bicarbonate	Jones et al. 1971
Anti-inflammatory properties	Lefebvre 1983
Stimulates bronchodilation	Lockey et al. 1969
Inhibition of erythropoiesis	Naets and Guns 1980
Antitumorogenic effect	Lefebvre 1983
Increases in bone density	Lefebvre 1983

Because of the known inotropic and chronotropic effects of glucagon, a study was designed specifically to examine the cardiovascular effects of rGlucagon in conscious beagle dogs.

Subcutaneous doses of 0, 0.02, 0.15, or 1 mg rGlucagon/kg were administered to conscious beagle dogs to determine cardiovascular effects. These doses exceed the typical therapeutic dosage range in man. A double latin square design was used; on four occasions separated by at least 3 days, 2 dogs per group were rotated randomly through the dose groups. Left ventricular pressure, systemic arterial pressure, heart rate, and electrocardiograms were collected for 4 hours after dose administration. The peak value of the first derivative of left ventricular pressure (dP/dt_{max}) was calculated as an index of left ventricular inotropic state. Systolic, diastolic, and mean arterial pressures and arterial pulse pressure were derived from the arterial pressure signal. Heart rate and left ventricular end-diastolic pressure were obtained from the ventricular pressure signal. Electrocardiograms were evaluated for abnormal rhythms, premature or ectopic beats, and for verification that P wave, P-R and Q-T intervals, and QRS durations were within normal ranges.

Treatment with 0.02 mg rGlucagon/kg produced no cardiovascular changes. Treatment with 0.15 or 1 mg rGlucagon/kg decreased pulse pressure and arterial pressure and increased heart rate. Left ventricular inotropic state was increased and left ventricular end-diastolic pressure was decreased in animals receiving 1 mg rGlucagon/kg. Electrocardiogram abnormalities were not observed at any dose level.

The decreased blood pressure and elevated heart rate observed in dogs after administration of doses ≥0.15 mg rGlucagon/kg were consistent with changes reported in the literature for both dogs and humans receiving animal-source glucagon. In a separate 2-week subchronic dog study, there were no electrocardiogram abnormalities or adverse effects on cardiac tissues, although a small increase in heart rate was observed following subcutaneous administration of 0.2 mg/kg/day. These effects are not believed to represent a safety issue, as the changes occurred only at relatively high doses and were not associated with electrocardiogram abnormalities. By comparison, the typical human subcutaneous dose of glucagon is 1 mg (less than 0.015 mg/kg for a 70-kg person).

The decreased blood pressure and elevated heart rate observed after administration of doses greater than 0.02 mg rGlucagon/kg were consistent with changes reported in the literature for both dogs and humans receiving animal-sourced glucagon. These effects were not considered toxicologically important, as the changes occurred only at relatively high doses and were not associated with electrocardiographic abnormalities.

TOXICOLOGY

Commercial animal-source glucagon is produced through an extraction process from beef and pork pancreas glands, followed by a high degree of purification. Recombinant glucagon (rGlucagon), on the other hand, is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by addition of the gene for glucagon.

Acute Toxicity

Glucagon was administered intravenously to fasted mice at doses up to 1000 mg/kg. The median lethal dose varied from 100 to 700 mg/kg. Solutions of glucagon became more toxic when stored at room temperature, due to an increase in viscosity of the highly concentrated solutions used. Signs of toxicity occurred shortly after treatment and included clonic convulsions and prostration; ptosis, leg weakness and hyperactivity.

Dogs given intravenous injections of 1 mg of glucagon (equivalent to 0.08 to 0.12 mg/kg) 4 times a day for two and a half days showed no overt signs of toxicity and no histologic changes were found. Neither were any signs of toxicity observed in a dog that received 8 hourly intravenous injections of 0.2 mg/kg of glucagon. In a dog that was injected 8 times in consecutive hours with intravenous doses of 1 mg/kg of glucagon, slight tremors that persisted through the course of treatment were seen following the second dose. This dog had moderate diarrhea and there was a temporary (2 hours) rise in blood sugar and fall in serum potassium but the dog appeared normal by the following day. Acute studies in rats and dogs showed that there was no detectable interaction between glucagon and propantheline bromide when the two compounds were administered 15 minutes apart. Rats received 0.8 mg/kg of glucagon subcutaneously followed by 12 mg/kg of propantheline bromide, and a second group of rats received the compounds in reverse order. Dogs were given 0.4 mg/kg of glucagon intramuscularly followed by 6 mg/kg of propantheline bromide, and in other dogs the order of compound administration was reversed. Mydriasis and some irritation at the injection sites, both attributed to propantheline bromide, were the only observations.

The acute toxicity of rGlucagon was studied in Fischer 344 rats; the summaries are tabulated in the table below:

Acute Toxicity Studies with rGlucagon

Species, Strain; No./Sex/Group; Age	Dose (mg/kg); Route of Administration	Duration of Obs	Parameters Evaluated	Observations
Rat, Fischer 344 5/sex/group; 9-10 weeks	0, 20 Subcutaneous	2 wk	Mortality; clinical observations; body weight; gross pathology	There were no deaths or signs of toxicity.
Rat, Fischer 344 5/sex/group; 10-11 weeks	0, 20 [a] Subcutaneous	2 wk	Mortality; clinical observations; body weight	There were no deaths or signs of toxicity.
Rat, Fischer 344 5/sex/group; 9-10 weeks	0, 20 Intravenous	2 wk	Mortality; clinical observations; body weight; gross pathology	There were no deaths. Decreased activity and ataxia occurred at 20 mg/kg. There were no effects on body weight or gross pathology changes.

Abbreviations: Tox. = Toxicology; No. = Number; Obs = Observations; wk = weeks.
[a] Material used was near expiration date.

Five rats/sex were administered a single intravenous or subcutaneous 20-mg/kg dose (10 mL/kg). An additional subcutaneous study was done using material that had been placed into vials approximately 18 months prior to testing. In each study, all animals survived the 2 week observation period after treatment. Following subcutaneous administration of 20 mg rGlucagon/kg, no signs of toxicity were observed in either study. However, immediately following intravenous administration of 20 mg rGlucagon/kg, decreased activity and ataxia were observed in all treated animals. These animals returned to normal within 1 hour after dosing and no additional evidence of toxicity was observed.

Subacute Toxicity

Thirty-seven dogs were constantly infused intravenously with glucagon: 5% dextrose solution for periods ranging from 2–29 days with glucagon doses ranging from 1.8–19 mg/kg/day. Food intake was diminished, and all dogs lost weight, but there were no other overt signs of toxicity. All dogs survived and appeared to be in a state of good health. Tachycardia commonly followed infusion of glucagon, but the compound produced no interruption in conductivity or increased irritability, and the dogs maintained a sinus rhythm. Erythrocytic and leukocytic parameters were unaffected by glucagon. A consistent fall in platelets and occasional increases in sedimentation rates were attributed to the infusion procedure. Serum calcium fell moderately, and total protein and BUN values declined. Moderate but not serious elevations in alkaline phosphatase were

common in the glucagon-infused dogs. No other clinical chemistry parameters (SGOT, CPK, free fatty acids, electrolyte, bilirubin, and LDH) appeared to be affected by glucagon.

Subchronic Toxicity

Studies of 2 weeks duration with daily dosing by the subcutaneous route have been conducted in rats and dogs (see table below).

Repeated Dose Toxicity Studies with rGlucagon

Species, Strain; No./Sex/Group; Age	Dose (mg/kg); Route of Admin.	Duration of Treatment	Parameters Evaluated	Observations
Rat, Fischer 344 10/sex/group; 6-7 weeks	0, 0.25, 1, 4 Subcutaneous	2 weeks	Survival; clinical obs; body weight; food consumption; ophthalmic examinations; plasma concentrations; hematology; clinical chemistry; urinalysis; organ weights; gross pathology and histopathology.	No adverse effects were observed at daily doses of 0.25, 1, or 4 mg/kg. Minor treatment related increases in liver weight and changes in hematology and clinical chemistry parameters unassociated with clinical or histopathologic findings occurred which were consistent with the pharmacologic effects of glucagon.
Dog, Beagle 3/sex/group; 10-16 months	0, 0.02, 0.06, 0.2 Subcutaneous	2 weeks	Survival; clinical obs; body weight; food consumption; ophthalmic examinations; ECGs; glucodynamics; hematology; clinical chemistry; urinalysis; organ weights; gross pathology and histopathology	No adverse effects at daily doses of 0.02, 0.06, or 0.2 mg/kg. Changes related to the pharmacology of glucagon included: increased serum glucose at all dose levels, an increase in heart rate at 0.2 mg/kg and modest increases in liver weight in females accompanied by mild hepatocellular hypertrophy but no clinical chemistry changes.

Abbreviations: Tox = Toxicology; Rpt = Report; No. = Number; Admin. = Administration; obs = observations; ECGs = electrocardiograms.

In summary, the effects observed in 2-week studies in rats and dogs, were considered to be related to the pharmacology of glucagon. These effects included increased serum glucose and increased liver weights not accompanied by adverse histopathologic changes. Increased liver weight in dogs and rats administered daily intravenous glucagon was also reported by Eistrup et al. (1993). The liver weight increases following repeated high doses of rGlucagon do not represent a significant human health risk considering the infrequent use of glucagon in any given individual. Other expected changes that were observed in dogs were soft stools, and increased heart rate.

***Myelocytic*:** Erythrocytic ratios were elevated in several dogs but bone marrow cellular morphology was normal and peripheral blood counts were unaffected. Thrombi and vasculitis of

the infusion veins and small vessels of the lungs were commonly seen during histological examination of the tissues but these findings were common to the infusion control animals and were considered to be the result of prolonged cannulation. The only significant histologic finding attributed to glucagon was the presence of foreign emboli in the small vessels in the lungs of some of the dogs. Although not numerous, the emboli which were assumed to be a form of glucagon were only found microscopically when several sections of the lungs were searched. The largest particle approximated 75 x 300 microns in size and did not assume the contour of the vessel lumen. The vessels remained patent and the emboli were unattached to the wall. Some of the particles were in the process of being removed by active phagocytosis. There was no evidence to indicate any serious physiological response to the emboli and respiration and circulation through the lung did not appear to be compromised.

Chronic Toxicity

Large doses of glucagon have been administered to normal rats and rabbits daily for six months without harmful effects. Transient hyperglycemia and glycosuria was demonstrated in dogs and cats receiving multiple daily injections or continuous infusions of glucagon in doses up to 9 mg/kg, for periods up to 108 days. There were no toxic effects or weight loss.

Mutagenicity Studies

The potential for mutagenic impurities in rGlucagon was tested using the Ames bacterial mutation assay (Table TX.3). Four *Salmonella typhimurium* strains dependent on exogenous histidine (TA1535, TA1537, TA98, and TA100) and one *Escherichia coli* strain dependent on exogenous tryptophan (WP2uvrA) were exposed to rGlucagon either in the presence (activated assay) or absence (nonactivated assay) of a rat liver microsome preparation. The tests were performed on histidine- or tryptophan-deficient media; growth of colonies on these media usually indicates a mutagenic event (reversion to histidine or tryptophan independence).

Table TX.3. Mutagenicity Studies

Study Type	Cell Type	Concentrations	Results
Bacterial mutation (Ames assay) - without metabolic activation	*Salmonella typhimurium* strains: TA1535, TA1537, TA98 and TA100; *Escherichia coli* strain: WP2uvrA	0.3125 - 5.0 mg/plate	Negative
Bacterial mutation (Ames assay) - with metabolic activation	*Salmonella typhimurium* strains: TA1535, TA1537, TA98 and TA100; *Escherichia coli* strain: WP2uvrA	0.3125 - 5.0 mg/plate	Negative[a]

[a] Increased revertants were observed, but were considered to result from histidine liberation rather than mutagenicity.

Tests with rGlucagon resulted in dose-related increases in colony counts for strains TA98 and TA100 in the activated assay. Increased colony counts were not observed in the nonactivated assays. Representative samples of treated TA98 and TA100 colonies grew when transferred to histidine-free media, indicating that the organisms were true revertants. The mechanism for the reversion, however, was apparently related to generation of histidine from rGlucagon and was not due to a mutagenic impurity. In order to ensure that the increased colony counts were not due to a mutagenic impurity, additional Ames assays were conducted using rGlucagon that had been subjected to additional purification. Purification by acid precipitation or reverse-phase chromatography did not change the ability of rGlucagon to increase colony counts. When material from a dialysis purification was tested, the permeate (containing any small molecules) did not increase colony counts, while the retentate (containing rGlucagon) continued to increase colony counts. These results indicated that no mutagenic impurities were present in the test article. Rather, the observed increases in colony counts can be explained based on the liberation of histidine, which is essential for the growth of TA98 and TA100, from rGlucagon. Concentration-dependent generation of histidine from rGlucagon under the conditions of the activated Ames assay was demonstrated in separate experiments. The high concentrations of rGlucagon in the test apparently provided sufficient histidine to allow continued cell divisions and subsequent formation of spontaneous revertants. Therefore, it was concluded that rGlucagon was not mutagenic in the Ames bacterial mutation assay.

REFERENCES

1. Amatuzio DS, Grande F, Wada S. Effect of Glucagon on the Serum Lipids in Essential Hyperlipemia and in Hypercholesterolemia. Metabolism 1962;11:1240-1249.
2. Amos J, Wranne L. Hypoglycemia in childhood diabetes II: Effect of subcutaneous or intramuscular injection of different doses of glucagon. Acta Pediatr Scand 1988;77:548-553.
3. Arai Y, Elrick H, Witten RA. Glucagon Treatment of Insulin Reactions. New Eng Jour of Med 1958;258:476-480.
4. Bowsher R, Woodworth J, Wilke A, Smith W, Yordy R, Lynch R. 1997. Characterization of dose, gender, and temporal response differences for recombinant glucagon in dogs. IDF Abstract, Diabetologia 40(Suppl. 1):A240.
5. Boyarsky S, Labay P. 1969. Ureteral motility. Ann Rev Med 20:383-394.
6. Braun M, Parker M. The Use of Glucagon in the Termination of Therapeutic Insulin Coma. The Amer Jour of Psychiatry 1959;115:814-815.
7. Bryan HG, Whitehouse FW. Glucagon for Treatment of Insulin Hypoglycemia: Its Use in the Patient with Diabetes. Amer Practitioner & Digest of Treatment 1959;10:1326-1330.
8. Cameron AJ, Phillips SF, Summerskill WHJ. Comparison of Effects of Gastrin, Cholecystokinin-pancreozymin, Secretin, and Glucagon on Human Stomach Muscle in vitro. Gastroenterol 1970;59:539-545.
9. Carsen GM, Finby N. Hypotonic Duodeography with Glucagon, Radiology 1976;118:529-533.
10. Carson MJ, Koch R. Clinical studies with Glucagon in Children. Journal of Pediatrics 1955;47:161-170.
11. Chernish SM, Miller RE, Rosenak BD, Scholz NE. Effects of Glucagon on Size of Visualized Human Gallbladder Before or After a Fat Meal. Gastroenterology 1972;62:1218-1226.
12. Chernish SM, Miller RE, Rosenak BD, Scholz NE. Hypotonic Duodenography with the Use of Glucagon. Gastroenterology 1972; 63:392,398
13. Chernow B, Reed L, Geelhoed GW, Anderson M, Teich S, Meyerhoff J, Beardsley D, Lake CR, Holaday JW. 1986. Glucagon: endocrine effects and calcium involvement in cardiovascular actions in dogs. Circ Shock 19:393-407.
14. Condon JR. Glucagon in the Treatment of Paget's Disease of Bone, British Med Jour 1971;4:719-721.
15. Cornblath M, et al. Studies of carbohydrate metabolism in the newborn: Effect of glucagon on concentration of sugar in capillary blood of newborn infant. Pediatrics 1958;21:885-892.
16. Crockford PM, et al. Glucagon, A "Contaminant", Comes of Age. CMAJ 1971;105:963.

17. Diamant B, Picazo J. 1983. Spasmolytic action and clinical use of glucagon. In: Lefebvre PJ, editor. Glucagon II. New York: Springer-Verlag. p 611-634.

18. Dotevall G, Kock NG. The Effect of Glucagon on Intestinal Motility in Man. Gastroenterol 1963;45:364-367.

19. Dyck WP, Texter EC, Lasater JM, Hightower NC. Influence of Glucagon on Pancreatic Secretion in Man. Gastroenterology 1970;58:532-539.

20. Editorial: Glucagon in Congestive Heart Failure. JAMA 1968;206:1078.

21. Elrick H, et al. Effects of Glucagon on Renal Function in Man. J Clin Endocrinol 1958;18:813-824.

22. Eistrup C, Hjortkjaer RK, Pickersgill N, Virgo DM, Woolley APAH. 1993. Glucagon produced by recombinant DNA technology: repeated dose toxicity studies, intravenous administration to CD rats and beagle dogs for four weeks. Pharmacol Toxicol 73:103-108.

23. Etzwiler DD. Effect of Glucagon Hydrochloride on Hypoglycemia of Juvenile Diabetics. The Jour of the Amer Med Assoc 1963;183:795-797.

24. Gibbs, et al. Use of Glucagon to terminate insulin reactions in diabetic children. Nebr Med J 1958;43:56-57.

25. Farah AD. 1983. Glucagon and the heart. In: Lefebvre PJ, editor. Glucagon II. New York: Springer-Verlag. p 563-573.

26. Feczko PJ, Haggar AM, Halpert RD. A reappraisal of upper gastrointestinal response to low-dose glucagon. CRC Crit Rev Diagn Imaging 1985;23(4):377-412.

27. Gilsanz V, Oteyza CP, Jose L. Glucagon vs Anticholinergics in the Treatment of Acute Pancreatitis. Arch Intern Med 1978;138:535-538.

28. Glucagon and Pheochromocytoma, Annals of Internal. Medicine. EDITORIAL 1970;73:851-852.

29. Gohel VK, Dalinka MK, Coren GC. Hypotonic Examination of the Colon with Glucagon. Rad 1975;115:1-4.

30. Harned RK, Stelling CB, Williams S, Wolf GL. Glucagon and Barium Enema Examinations: A Controlled Clinical Trial. The Amer Jour of Roentgenol, Radium Therapy and Nuclear Medicine 1976;126:981-984.

31. Haunz EA. Feigned Insulin Reactions in Diabetic Children Prevented by Glucagon. Lancet 1962;82:263-267.

32. Hall-Boyer K, Zaloga GP, Chernow B. Glucagon: Hormone or therapeutic agent? Critical Care Medicine 1984;7:584-589.

33. Helmer OM, Kirtley WR, Ridolfo AS. Clinical and Metabolic Changes Induced by Glucagon in Patients with Rheumatoid Arthritis. J Lab and Clin Med 1957;50:824.

34. Hug G. Glucagon Tolerance Test in Glycogen Storage Disease. The Jour of Ped 1962;60:545-549.

35. Jones RS, Geist RE, Hall AD. 1971. The choleretic effects of glucagon and secretin in the dog. Gastroenterol 60:64-68.

36. Kimball CP, Murlin JR. Aqueous Extracts of Pancreas: III. Some Precipitation Reactions of Insulin. J Biol Chem 1923;58:337-346.

37. Kirtley WR, Peck FB. Glucagon-The Hyperglycemic Glycogenolytic Factor. The Journal of the Indiana State Med Assn 1958;51:1302-1398.

38. Klein SW, Morch JE, Mahon WA. Cardiovascular Effects of Glucagon in Man. Canadian Medical Assoc Jour 1968;98:1161-1164.

39. Kolanowski J. 1983. Influence of glucagon on water and electrolyte metabolism. In: Lefebvre PJ, editor. Glucagon II. New York: Springer-Verlag. p 525-536.

40. Kreel L. Pharmaco-Radiology in Barium Examinations with Special Reference to Glucagon. The Brit J of Rad 1975;48:691-703.

41. Lawrence AM. Glucagon in Medicine: New Ideas for an Old Hormone. Med Clin N Amer 1970;54:183-190.

42. Lefebvre PJ. 1983. Miscellaneous pharmacologic effects of glucagon. In: Lefebvre PJ, editor. Glucagon II. New York: Springer-Verlag. p 667-672.

43. Linhart JW, Barold SS, Cohen LS, Hildner FJ, Samet P. Cardiovascular Effects of Glucagon in Man. A J Cardiology 1968;22:706-710.

44. Lin TM, Evans DC, Spray GF. 1973. Mechanism studies on gastric inhibition by glucagon: failure of KCl and adrenergic blocking agents to prevent its action. Arch Int Pharmacodyn Therap 202:314-324.

45. Lockey SD, Reed CE, Ouellette JJ. 1969. Bronchodilating effect of glucagon in asthma. J Allerg 43:177-178.

46. Marks V. Glucagon in diagnosis and treatment of hypoglycemia. In: Lefèbvre PJ Eds. Glucagon II. Springer Verlag 1983:645-666.

47. Miller RE, Chernish SM, Rosenak BD, Rodda BE. Hypotonic Duodenography with Glucagon. Rad 1973;108:35-42.

48. Miller RE, Chernish SM, Skucas J, Rosenak BD, Rodda BE. Hypotonic Colon Examination with Glucagon. Radiology 1974;113:555-562.

49. Naets JP, Guns M. 1980. Inhibitory effect of glucagon on erythropoiesis. Blood 55:997-1002.

50. Necheles H, Sporn J, Walker L. Effect of Glucagon on Gastrointestinal Motility. Am J Gastro 1966;45:34-39.

51. Parmley WW, Glick G, Sonnenblick EH. 1968. Cardiovascular effects of glucagon in man. N Engl J Med 279:12-17.

52. Parmley WW, Sonnenblick EH. Editorial, A Role for Glucagon in Cardiac Therapy. Am J Med Sc 1969;258:224-229.

53. Pearson T. Glucagon as a Treatment of Severe Hypoglycemia: Safe and Efficacious but Underutilized. The Diabetes Educator 2008; 34: 128-134.

54. Penick SB, Hinkle LE Jr. 1957. Depression of food intake induced in healthy subjects by glucagon. N Engl J Med 96:518-520.

55. Poser H, Baier J. Comparative Pharmaco-Dynamic Colon Double Contrast Examination with Glucagon and Atropine. Radiol Diagn 1977;18:355-358.

56. Ratcliffe KM, Esophageal Foreign Bodies. AFP 1991;3:824-831.

57. Schmitt JK. Indomethacin and hypoglycemia. Diabetes Care 1987;10(6):790.

58. Sheps S, Maher FT. Histamine and Glucagon Tests in Diagnosis of Pheochromocytoma. JAMA 1968;205:79-83.

59. Shipp JC, Delcher HK, et al. Treatment of insulin hypoglycemia in diabetic campers. Diabetes 1964;13:645-648.

60. Sporn J, Necheles H. 1956. Effect of glucagon on gastrointestinal motility. Am J Physiol 187:634.

61. Staub A, Sinn L, Behrens OK. Purification and Crystallization of Hyperglycemic Glycogenolytic Factor (HGF). Science 1953;117:628-629.

62. Staub A, Sinn L, and Behrens OK. The Glucagon Content of Crystalline Insulin Preparation. J Biol Chem 1955;214:619-632.

63. Stunkard AJ, Van Itallie TB, Reis BB. 1955. The mechanism of satiety: effect of glucagon on gastric hunger contraction in man. Proc Soc Exp Biol Med 89:258-261.

64. Taylor I, Duthie HL, Cumberland DC, Smallwood R. Glucagon and the Colon. GUT 1975;16:973-978.

65. Williams JF, Childress RH, Chip JN, and Border JF. Hemodynamic Effects of Glucagon in Patients with Heart Disease. Circulation 1969;XXXIX:38-47.

66. Weinstein RS. Recognition and Management of Poisoning with Beta-Adrenergic Blocking Agents. Ann Emerg Med 1984;13:1123-1131.

67. Zaritsky AL, Horowitz M, Chernow B. Glucagon antagonism of calcium channel blocker-induced myocardial dysfunction. Critical Care Medicine 1988;3:246-251.

PART III: CONSUMER INFORMATION

GLUCAGON
(Glucagon for Injection, rDNA origin)

This leaflet is part III of a three-part "Product Monograph" published when GLUCAGON was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GLUCAGON. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medicine, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:

Notice: Recombinant glucagon replaces the animal sourced glucagon. The structure and activity of recombinant glucagon is identical to animal sourced glucagon.

GLUCAGON (glucagon for injection, rDNA origin) and the GLUCAGON kit are used for emergency treatment of severe hypoglycemia (unconsciousness due to low blood glucose) which may occur in diabetic patients treated with insulin.

Symptoms of low blood glucose include:

- sweating
- dizziness
- palpitations
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressive mood
- irritability
- abnormal behaviour
- unsteady movement
- personality changes

If not treated, the patient may progress to severe hypoglycemia, which can include:

- disorientation
- unconsciousness
- seizures
- death
- palpitations

The occurrence of early symptoms calls for prompt and, if necessary, repeated administration of some form of carbohydrate, for example, candy, orange juice, corn syrup, honey or lumps of sugar. If improvement does not occur or if administration of carbohydrate is impossible, GLUCAGON should be given. Glucagon, a naturally occurring substance produced by the pancreas, is helpful because it enables the patient to produce his/her own blood glucose to correct the hypoglycemic state. The patient can then take carbohydrates by mouth. In this way, severe hypoglycemic reactions can be avoided, and diabetic control will be easier to accomplish. Patients who are unable to take sugar orally, or who are unconscious, require an injection of GLUCAGON or should be treated with intravenous administration of glucose at a medical facility. *The physician should always be notified promptly whenever severe hypoglycemic reactions occur.*

GLUCAGON is an emergency drug to be used only under the direction of a physician. People in regular contact with a person with diabetes should become familiar with the proper use of this medication before an emergency arises.

What it does:
GLUCAGON (glucagon for injection, rDNA origin) is a high blood sugar agent that causes an increase in blood glucose concentration. Glucagon acts on liver glycogen, converting it to glucose.

When it should not be used:
GLUCAGON (glucagon for injection, rDNA origin) should not be used in patients with known hypersensitivity to it or in patients with pheochromocytoma (adrenal gland tumour).

What the medicinal ingredient is:
Glucagon (rDNA origin)

What the important nonmedicinal ingredients are:
Glycerin (in diluting solution), lactose monohydrate, and hydrochloric acid (pH adjuster).

What dosage forms it comes in:
GLUCAGON (glucagon for injection, rDNA origin) comes in a powder form with accompanying diluting solution.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

GLUCAGON should be given only if the patient is unconscious or unresponsive and unable to ingest oral glucose. After intramuscular injection, the patient will normally respond within 10 minutes. If the patient does not respond within 10 minutes, intravenous glucose must be administered as soon as an IV access can be established.

When the patient has responded to the treatment, give oral carbohydrate to restore liver glycogen and prevent relapse of hypoglycemia.

Because glucagon is of little help in states of starvation, adrenal insufficiency, or chronic hypoglycemia, intravenous glucose should be used for treatment of hypoglycemia in those conditions.

BEFORE you use GLUCAGON talk to your doctor or pharmacist if:

- you are fasting, have low levels of adrenaline, chronic low blood sugar or low levels of liver glycogen due to excessive consumption of alcohol
- you have chronic hypoglycemia
- you have an adrenal gland tumour
- you have an insulin releasing tumour

- you are pregnant or breast feeding
- you are allergic to glucagon, lactose or glycerin

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Glucagon include:

- insulin
- indomethacin
- warfarin

PROPER USE OF THIS MEDICATION

Usual dose:

- **Adults:** 1 mg/1 mL (1 unit/1 mL)
- **Children weighing more than 20 kg:** 1 mg/mL (1 unit/1 mL)
- **Children weighing less than 20 kg:** 0.5 mg/1 mL (0.5 unit/1 mL)

Doses must be given by subcutaneous, intramuscular, or intravenous injection.

Note: The patient with diabetes may also be in coma from diabetic acidosis (hyperglycemia) rather than from hypoglycemia and in such cases will not respond to glucagon. These patients require immediate medical attention for the treatment of the diabetic acidosis. Contact the physician immediately.

Overdose:

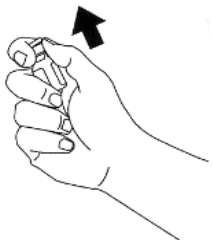
If overdosage occurs, it would be associated with nausea, vomiting, stomach relaxation and diarrhea.

Immediately contact the Regional Poison Control Centre or your doctor or go to the nearest hospital emergency department.

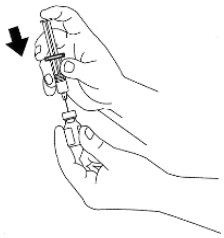
TO PREPARE GLUCAGON FOR USE:

Note: GLUCAGON should not be prepared for injection until emergency arises. The expiry date should be checked regularly and a new kit purchased when approaching expiry date. Do not use this kit after the date stamped on the outside of the box. GLUCAGON should be used immediately after mixing with diluent.

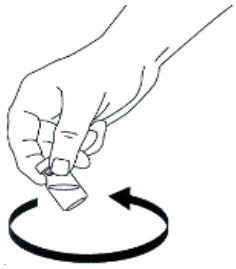
1. Remove the flip-off seal from the bottle of GLUCAGON.



2. Remove the needle protector from the syringe, and inject the entire contents of the syringe into the bottle of GLUCAGON. DO NOT REMOVE THE PLASTIC CLIP FROM THE SYRINGE. Remove syringe from the bottle.



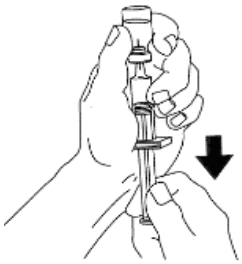
3. Swirl bottle gently until GLUCAGON dissolves completely. GLUCAGON SHOULD NOT BE USED UNLESS THE SOLUTION IS CLEAR AND OF A WATER-LIKE CONSISTENCY.



TO ADMINISTER GLUCAGON

Use Same Technique as for Injecting Insulin

1. Using the same syringe, hold bottle upside down and, making sure the needle tip remains in solution, withdraw all of the solution (1 mg mark on syringe) from bottle. The plastic clip on the syringe will prevent the plunger from being pulled out of the syringe; however, if the plastic plunger rod separates from the rubber stopper, simply reinsert the rod by turning it clockwise.
2. The usual adult dose is 1 mg (1 unit). For children weighing less than 44 lb (20 kg), give 1/2 adult dose (0.5 mg). For children, withdraw ½ of the solution from the bottle (0.5 mg mark on syringe). DISCARD UNUSED PORTION.



USING THE FOLLOWING DIRECTIONS, INJECT GLUCAGON IMMEDIATELY AFTER MIXING.

1. Cleanse injection site on buttock, arm, or thigh with alcohol swab.
2. Insert the needle into the fatty tissue under the cleansed injection site, and inject all of the GLUCAGON solution. THERE IS NO DANGER OF OVERDOSE. Apply light pressure at the injection site, and withdraw the needle. Press an alcohol swab against the injection site.
3. Turn the patient on his/her side. When an unconscious person awakens, he/she may vomit. Turning the patient on his/her side will prevent him/her from choking.

FEED THE PATIENT AS SOON AS HE/SHE AWAKENS AND IS ABLE TO SWALLOW. Give the patient a fast-acting source of sugar (such as a regular soft drink or sweetened orange juice) and a long-acting source of sugar (such as crackers and cheese or a meat sandwich). If the patient does not awaken within 15 minutes, give another dose of GLUCAGON and CALL A PHYSICIAN IMMEDIATELY.

CAUTION: Low blood glucose may cause convulsions.

What to tell your friends, family, caregiver or co-workers:

Your doctor may have given you GLUCAGON so that your friends or relatives can give you the injection, if you become severely hypoglycemic (unconsciousness due to low blood sugar) and cannot take sugar by mouth. Make sure they know:

- how to use GLUCAGON and where it is kept before an emergency arises.
- They must inject GLUCAGON into a muscle.
- You must be given a high sugar snack like sweets, biscuits or fruit juice after you have responded to treatment (as soon as you are able to take it). This is because glucagon depletes glycogen stores. The high sugar snack will prevent relapse of the hypoglycemia.
- After using GLUCAGON, you or someone else must contact your doctor or healthcare provider. You need to find out why you had severe hypoglycemia and how to avoid it happening again.

For management of a suspected drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

GLUCAGON is relatively free of side effects except for occasional nausea, vomiting, and generalized allergic reactions.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare (less than 1 in 10, 000)	Nausea	✓		
	Vomiting	✓		
	Allergic Reaction (including hives, respiratory distress and low blood pressure)		✓	

This is not a complete list of side effects. For any unexpected effects while taking GLUCAGON, contact your doctor or pharmacist.

HOW TO STORE IT

Keep all medicines out of reach of children.

GLUCAGON should be stored as follows:

Before Reconstitution: Prior to reconstitution, Vials of GLUCAGON and prefilled Hyporets of Diluting Solution may be stored at room temperature (15° to 30°C).

Reconstituted Solutions: GLUCAGON should be used immediately after reconstitution. **Discard any unused portion.**

The expiry date of this medicine is printed on the package label. Do not use past expiry date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  – Fax toll-free to 1-866-678-6789, or
  – Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at www.lilly.ca

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

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