PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

GLUCAGEN®

and

GLUCAGEN® HYPOKIT

glucagon

ATC Code: H04AA01

Powder and solvent for solution for injection, 1 mg, Intramuscularly

Hyperglycemic Agent

Manufactured by: Novo Nordisk Canada Inc.
101-2476 Argentia Road
Mississauga, Ontario
L5N 6M1 Canada

Distributed by: Paladin Labs Inc.
St-Laurent, QC H4M 2P2

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

GlucaGen® / GlucaGen® HypoKit (glucagon) **is indicated for:**

- For the treatment of severe hypoglycemic reactions which may occur in the management of insulin treated persons with diabetes mellitus, when unconsciousness precludes oral carbohydrates.

The use of GlucaGen® is approved for administration by i.m. injection.

1.1 Pediatrics

Pediatrics (**<18 years of age):** Pediatrics between birth and 16 years of age were not studied in the clinical studies. (See 7.1 Special Populations)

1.2 Geriatrics

Geriatrics (≥65 years): No data available.

2 CONTRAINDICATIONS

GlucaGen® is contraindicated in patients with:

- Pheochromocytoma
- Hypersensitivity to glucagon or to any ingredient in the formulation including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, and COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

GlucaGen® 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, acute or chronic alcohol use, adrenal insufficiency, or chronic hypoglycemia, intravenous glucose should be used for the treatment of hypoglycemia in these conditions (7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

GlucaGen® and GlucaGen® HypoKit should be reconstituted with the accompanying diluent following the detailed directions contained within the section 4.4 Administration.

4.2 Recommended Dose and Dosage Adjustment

GlucaGen® and GlucaGen® HypoKit:

Dosage for adult patients:
Administer 1.0 mg.

Dosage for paediatric patients:
Administer 1.0 mg (children above 25 kg or older than 6-8 years) or 0.5 mg (children below 25 kg or younger than 6-8 years).

Administer by intramuscular injection. The patient will normally respond within 10 minutes. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycemia. If the patient does not respond within 10 minutes, intravenous glucose should be given.

Medical consultation is required for all patients with severe hypoglycemia.

Caution: Although glucagon may be used for the treatment of hypoglycemia for the patient during an emergency, the physician must still be notified when hypoglycaemic reactions occur so that the dose of insulin and oral antidiabetic medication may be adjusted more accurately.

4.3 Reconstitution

Reconstitution of the parenteral GlucaGen® product:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
2.0 mL	1.1 mL	1.0 mL	1 mg/mL

Before reconstitution the compacted powder should be a white or nearly white powder. The solvent should be clear and colourless without particles.

The reconstituted solution forms an injection of 1 mg (1 IU) per mL to be administered by intramuscular injection.

4.4 Administration

If fibril formation (viscous appearance) or solid particles are present in the solution, it must not be used. Discard any unused portion.

The reconstituted solution should be administered immediately after preparation.

GlucaGen® (glucagon):

Draw up the Water for Injection (1.1 mL) in a disposable syringe. Inject the Water for Injections into the vial containing the freeze-dried glucagon. Shake the vial gently until the glucagon is completely dissolved and the solution is clear. Withdraw the solution back into the syringe.

Any unused product or waste material should be disposed of in accordance with local requirements.

GlucaGen® HypoKit (glucagon):

Inject the Water for Injections (1.1 mL) into the vial containing the freeze-dried glucagon. Shake the vial gently until the glucagon is completely dissolved and the solution is clear. Withdraw the solution back into the syringe.

5 OVERDOSAGE

Glucagon has a short half-life of approximately 3-6 minutes. Therefore, treatment of overdose is symptomatic - primarily for nausea, vomiting and hypokalemia.

Hyperglycemia may also be a symptom of overdose.

In case of suspected overdosing (i.e. above therapeutic dosages), the serum potassium may decrease and should be monitored and corrected, if needed.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscularly	Lyophilized powder for injection/1 mg	Hydrochloric acid and/or sodium hydroxide (pH adjusters), lactose monohydrate, and water for injection.

Description

GlucaGen® (glucagon):
GlucaGen® 1 mg/ mL vial is supplied as a sterile, compacted, freeze-dried white powder of glucagon in a 2 mL vial and accompanying solvent also in a 2 mL vial. Glucagon powder is reconstituted with 1.0 mL of water for injections (WFI), forming a solution of 1 mg (1 IU) glucagon and 107 mg of lactose monohydrate in each mL prior to use. It is to be administered intramuscularly (into the muscle).

One stoppered glass vial contains 1 mg glucagon corresponding to 1 mg glucagon/ mL after reconstitution.

The vials are provided with a tamperproof plastic cap, which must be removed before use.

GlucaGen® HypoKit (glucagon):
GlucaGen® HypoKit 1 mg/ mL vial is supplied as a sterile, compacted, freeze-dried white powder of glucagon in a 2 mL vial and accompanying solvent in a 1.5 mL disposable syringe. Glucagon powder is reconstituted with 1.0 mL of water for injections (WFI), forming a solution of 1 mg (1 IU) glucagon and 107 mg of lactose monohydrate in each mL prior to use. It is to be administered intramuscularly (into the muscle).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: HEALTH PROFESSIONAL INFORMATION.

General
To prevent relapse of hypoglycemia, oral carbohydrates should be given to restore the liver glycogen when the patient has responded to the treatment.

Lack of Efficacy in Patients with Decreased Hepatic Glycogen
GlucaGen® for injection, rDNA origin, is helpful in treating hypoglycemia only if sufficient liver glycogen is present. Patients in states of starvation (e.g. due to prolonged fasting), with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of liver glycogen for GlucaGen® administration to be effective.

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

Glucagonoma and Insulinoma

Glucagon reacts antagonistically towards insulin and caution should be observed if GlucaGen® is used in patients with insulinoma. Caution should also be observed in patients with glucagonoma.

Due to the instability of GlucaGen® in solution, the product should be used immediately after reconstitution and must not be given as an intravenous infusion.

Carcinogenesis and Mutagenesis
No carcinogenicity studies have been conducted.

The potential for genotoxicity of glucagon (rDNA origin) has been evaluated using a series of recognized *in vitro* and *in vivo* assays for mutagenic-genotoxic activity and results indicate that glucagon (rDNA origin) should be considered non mutagenic. (See 16 NON-CLINICAL TOXICOLOGY)

Cardiovascular
In high concentrations, glucagon exerts positive inotropic and chronotropic effect and may therefore cause tachycardia and acute hypertensive reactions.

Driving and Operating Machinery
No studies on the effects on the ability to drive and use machines have been performed. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine
Substantial Increase in Blood Pressure in Patients with Pheochromocytoma
GlucaGen® is contraindicated in patients with pheochromocytoma. Exogenous glucagon also stimulates the release of catecholamines. In the presence of pheochromocytoma, GlucaGen® can cause the tumour to release catecholamines, which results in a sudden and marked increase in blood pressure (See 2 CONTRAINDICATIONS).

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

Patient Education
Because GlucaGen® HypoKit is designed to be administered in emergency situations to the patient by relative(s), where a high level of stress is likely, it is imperative that the kits are easy to find and easy to use. It is therefore important that the patient is instructed to make sure that family, friends and co-workers know when and how to use GlucaGen® HypoKit. Specific directions for reconstitution and use should also be provided along with the GlucaGen® HypoKit.

Specific instructions on the use of GlucaGen® should be given to patients at risk of hypoglycemia unawareness, including elderly.

Sensitivity/Resistance
Glucagon is a protein in which hypersensitivity reactions may occur in rare events. Generalized allergic reactions including urticaria, respiratory distress, and hypotension (anaphylactic reaction/shock), have been reported in patients who received glucagon. GlucaGen® is contraindicated in patients with a prior hypersensitivity reaction (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

Well-controlled studies in pregnant women have not been performed with recombinant glucagon. GlucaGen® should be used during pregnancy only if oral carbohydrates cannot be administered (See 10 CLINICAL PHARMACOLOGY). Glucagon does not cross the human placenta barrier. The use of glucagon has been reported in pregnant women with diabetes and no harmful effects are known with respect to the course of pregnancy and the health of the fetus and neonate.

Animal reproduction studies have not been conducted with GlucaGen®.

7.1.2 Breast-feeding

It is not known whether GlucaGen® is excreted in human milk. Glucagon is quickly cleared from the bloodstream by the liver ($T_{½}$= 3-6 min); thus the amount excreted in the milk of nursing mothers following treatment of severe hypoglycemic reactions will be extremely small. As glucagon is degraded in the digestive tract and cannot be absorbed in its intact form, it will not exert any metabolic effect in the child.

7.1.3 Pediatrics

The use of GlucaGen® in pediatric patients (>25 kg or older than 6-8 years) has been reported to be safe and effective (See 1 INDICATIONS).

7.1.4 Geriatrics

No data available. Elderly patients on insulin may also be candidates for glucagon, as they may have hypoglycemic unawareness simply because of the aging process.

Patients with type 2 diabetes

When deciding about the use of glucagon for the patient with type 2 diabetes, consider those with a long duration of diabetes and/or insulin treatment. Those with advanced type 2 diabetes have a similar decline in counter-regulatory hormones as do those with type 1 diabetes.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of GlucaGen® has been assessed in six clinical studies after up to 3 doses of glucagon.

Adverse reactions are very rare except for occasional nausea and vomiting which may also occur with hypoglycemia.

Generalized allergic reactions including urticaria, respiratory distress, and hypotension (anaphylactic reaction/shock), have been reported in patients who received glucagon (See 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Common Adverse Events Reported in Clinical Studies

For summary of the most frequently reported (>1% of subjects) adverse events, see Table 1.

Table 1: Number of Common Adverse Events in all clinical studies

Body System AE preferred Term	1 mg GlucaGen® N=187 N (%)	1 mg pancreatic glucagon [a] N=102 N (%)
Body as a whole - General Disorders		
Tired	2 (1.1)	4 (3.92)
Sweating	2 (1.1)	-
Trembling (tremor)	2 (1.1)	-

Central & Peripheral Nervous System Disorders		
Headache	5 (2.7)	3 (2.9)
Dizziness	26 (13.9)	17(16.7)
Gastro-intestinal System Disorders		
Nausea	49 (26.2)	27 (26.5)
Vomiting	7 (3.7)	6 (5.9)

[a] Adverse events reported form 6 different clinical trials, some of which had a pancreatic glucagon control group

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions were reported at an incidence of < 1%:
Body as a whole General Disorders: Anxiety, blurred vision, dry mouth, generally unwell, hungry, leg pain, malaise, reactive hypoglycemia, slightly apathetic, thirsty, trembling, tremor, very hungry, very tired, weakness.

Cardiovascular Disorders: Arrhythmia, myocarditis, pericarditis, pulmonary embolism, slight palpitation, tachycardia, unrest and palpitation, vasovagal.

Gastrointestinal System Disorders: Slightly troubled stomach.

Respiratory Disorders / Infections and Infestations: Bronchospasm, pneumonia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

8.5 Post-Market Adverse Reactions

Frequencies of undesirable effects considered related to treatment with GlucaGen® during clinical trials and/or post-marketing surveillance survey is presented below. Undesirable effects which have not been observed in clinical trials, but have been reported spontaneously are presented as "very rare". During marketed use reporting of adverse drug reactions is very rare (≤ 1/10,000). However, post-marketing experience is subject to under-reporting and this reporting rate should be interpreted in that light.

Table 2: Post-marketing experience

Body system	Subject incidence	Adverse drug reaction

Immune system disorders	Very rare ≤ 1/10,000	Hypersensitivity reactions including anaphylactic reaction/shock
Gastrointestinal disorders	Common > 1/100 and < 1/10 Uncommon >1/1000 and ≤ 1/100 Rare > 1/10,000 and ≤ 1/1000	Nausea Vomiting Abdominal pain
General disorders and administration site conditions	Unknown	Injection site reactions

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions between GlucaGen® (glucagon) and other drugs are not known, when GlucaGen® is 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.

Beta-blockers: Patients taking beta-blockers might be expected to have a greater increase in both pulse and blood pressure, an increase of which will be temporary because of glucagon's short half-life. The increase in blood pressure and pulse rate may require therapy in patients with coronary artery disease.

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

9.3 Drug-Behavioural Interactions

Behavioral interactions have not been established.

9.4 Drug-Drug Interactions

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

Sulfonylurea: Although the use of glucagon in patients taking a sulfonylurea should work acutely, the pharmacokinetic characteristics of sulfonylurea will result in remaining systemic concentrations for a long time and thus can cause significant and prolonged hypoglycemia. The preferred treatment of severe hypoglycemia in patients taking sulfonylurea is therefore the administration of glucose by i.v. bolus injection followed by continuous i.v. infusion until the end of the pharmacologic effects of the sulfonylurea.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratories have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

GlucaGen® is a polypeptide hormone identical to human glucagon, which is manufactured by recombinant DNA technology and has the same molecular structure as animal-sources glucagon.

Glucagon acts to increase the concentration of glucose in the blood by releasing glucose from storage in the liver. Parenteral administration of glucagon relaxes also smooth muscle of the stomach, duodenum, small bowel, and colon.

10.2 Pharmacodynamics

The pharmacodynamics of GlucaGen® (glucagon) has been determined in a two part crossover, double-blind comparative bioavailability study in 12 healthy male adult subjects (Study 1). Plasma glucagon, insulin, blood glucose and C-peptide levels after were measured after i.m. injection of 1 mg GlucaGen® (glucagon) and 1 mg pancreatic glucagon formulations.

Study 1 showed a rapid rise in circulating glucagon levels following an i.m. injection of 1 mg glucagon with a mean plasma level of 3612.6 pg/mL at 0.167hr after pancreatic glucagon and 3975.38 pg/mL at 0.167hr after GlucaGen®.

The plasma levels of insulin increased in parallel with C-Peptides to achieve a mean plasma level of 62.25 (±53.63) mU/L at a median time of 0.417 hr following injection of pancreatic glucagon. After GlucaGen® administration, the plasma insulin concentration level increased to

85.79 (±101.46) mU/L at a median time of 0.5 hr.

The plasma glucose levels increased rapidly after injection of both formulations to a maximum of 9.06 mmol/L (±1.29) and 8.62 mmol/L (±0.90) following pancreatic glucagon and GlucaGen® injections, respectively.

The c-peptide plasma levels increased, from a mean pre-dose value of 780.42 pmoles/L to a mean value of 2444.55 pmoles/L at 0.5hr after pancreatic glucagon and from a mean pre-dose value of 575.83 pmoles/L to a mean value of 2289.09 pmoles/L at 0.833hr after GlucaGen®.

The plasma levels of glucose, c-peptide and insulin returned to pre-dose values at about 1.5hr after injection of both pancreatic glucagon and GlucaGen®.

10.3 Pharmacokinetics

A pharmacokinetic open-labelled study was performed to provide C_{max} and AUC $_{0\text{-}4hrs}$ for GlucaGen® after a single i.m. dose in 12 healthy adult males for pharmacokinetic properties and in 20 subjects for safety evaluation (Study 2A).

A summary of the pharmacokinetic results for study 2A is presented in Tables 3.

Table 3: Summary of Glucagon Pharmacokinetic Parameters following the i.m. administration of GlucaGen® to healthy volunteers

Study	Dose	C_{max} (mg/min) Mean (SD)	T_{max} (min) Mean (SD)	$AUC_{0\text{-}360}$ (mg) Mean (SD)	$AUC_{0\text{-}4hrs}$ (pg*min/mL) Mean (SD)
2A[a]	1 mg GlucaGen®	1627.5 (730.4)	17.9 (23.4)	----	93992.4 (43682.0)

[a]Values for study 2A =average of 3 baseline readings subtracted from all samples.

Absorption: CLINICAL PHARMACOLOGY- Pharmacokinetics and DETAILED PHARMACOLOGY- Clinical Pharmacology

Distribution: The volume of distribution of glucagon is approximately 0.2 L/kg.

Metabolism: Metabolic clearance rate of glucagon in humans is approximately 10 mL/kg/min. It is degraded enzymatically in the blood plasma and in the organs to which it is distributed. The liver and kidney are major sites of glucagon clearance, each organ contributing about 30% to the overall metabolic clearance rate.

Elimination: Following a 1 mg i.m. injection of GlucaGen®, the half-life was approximately 3-6 minutes. The clearance of glucagon is approximately 19 mL/ min*kg. Glucagon is eliminated in tissues, plasma, liver, and the kidneys however; the main route of elimination has not yet been determined.

Duration of Effect: Onset of effect occurs within 1 minute after an intravenous injection. The onset of effect occurs within 5-15 minutes after an intramuscular injection, with the duration of 10-40 minutes. When used in treatment of severe hypoglycaemia, an effect on blood glucose is usually seen within 10 minutes.

Special Populations and Conditions

See 7.1 Special Populations.

DETAILED PHARMACOLOGY

Glucagon acts to increase the concentration of glucose in the blood by releasing glucose from storage in the liver. Glucagon also exhibits the following pharmacological effects:

Gastrointestinal Activity	
Gastric	Inhibits tone, mobility and acid output
Biliary	Increases bile flow
Pancreatic	Decreases secretion of digestive enzymes
Blood flow	Increased in the abdominal region
Duodenum	Inhibits tone and motility
Small and large Intestine	Inhibits tone and motility
Other activities	
Adrenal	Releases catecholamines
Cardiac	Has a positive chronotropic and inotropic action
Calcium	Slightly reduces the serum levels
Adipose Tissues	Releases fatty acids

Glucagon is a hyperglycemic agent that mobilizes hepatic glycogen, which is released into the blood as glucose. Glucagon will not be effective in patients whose liver glycogen is depleted. For that reason, glucagon has little or no effect when the patient is fasting, or is suffering from adrenal insufficiency, chronic hypoglycemia or alcohol induced hypoglycemia.

Glucagon, unlike adrenaline, has no effect upon muscle phosphorylase and therefore cannot assist in the transference of carbohydrate from the much larger stores of glycogen that are present in the skeletal muscle.

The release of catecholamines is stimulated by glucagon, and in the presence of phaeocromocytoma, glucagon can cause the tumour to release large amounts of catecholamines which will cause an acute hypertensive reaction.

Animal Pharmacology

Glucagon manufactured by genetic engineering (rDNA origin) is demonstrated to have the same biological property as the 1st International Standard of pancreatic glucagon concerning the primary pharmacological hyperglycemic effect.

The other pharmacological effects on the cardiovascular system and respiration have shown i.v. administration of 0.03 mg/kg body wt. and 0.3 mg/kg body wt. glucagon, (rDNA origin), or pancreatic glucagon to decrease the systemic arterial blood pressure in association with increased heart rate and cardiac output in the rat, cat and pig, respectively. These well-known circulatory events reflect a direct vascular smooth muscle relaxation caused by glucagon combined with positive and inotropic and chronotropic effects of the peptide.

The affect of glucagon, (rDNA origin) on smooth muscle activity was investigated using the isolated guinea-pig ileum preparation. Glucagon (ge) concentrations 0.1, 1.0 or 10.0 ?g/mL did not exhibit contractions or influence contractions induced by 1 mg/mL acetylcholine or 1 mg/mL histamine.

Twenty female rats were hydrated with 10 mL water per-orally by gavage and dosed i.v. with placebo, glucagon, (rDNA origin), and pancreatic glucagon of 0.03 and 0.3 mg/kg. No statistically significant differences were seen between the placebo, and groups treated with either formulation of glucagon. Glucagon, (rDNA origin), was therefore found not to interfere with the diuresis.

Studies in NMRI mice have revealed, glucagon, (rDNA origin), at doses of 0.03 and 0.3 mg/kg i.v. have no influences on the sleeping time after i.v. administration of 100 mg/kg hexobarbital or 4.5 mg/kg ethanol.

Clinical Pharmacokinetics:

See **10.3 Pharmacokinetics.**

Clinical Pharmacology

Ahrén *et. al.* (1987) reported a study in which 18 non-diabetic subjects received 0.25 mg, 0.50 mg or 1.0 mg intravenously and the plasma levels of insulin, C-peptide and glucose were determined. This study demonstrates, glucagon stimulates insulin secretion through both direct (from the ß-cells) and indirect (plasma glucose) effects; that following glucagon injection, approximately 65 % of the secreted insulin is extracted by the liver and that the dose level of 0.5 mg glucagon administered intravenously is the optimal dose level for the stimulation of insulin secretion.

11 STORAGE, STABILITY AND DISPOSAL

GlucaGen® (glucagon):
Prior to reconstitution, the shelf life of the product is 3 years. GlucaGen® should be stored at a temperature not exceeding 2-8°C. The sealed container should be protected from light and freezing should be avoided.

The reconstituted GlucaGen® should be used immediately after preparation. Any unused product or waste material should be disposed of in accordance with local requirements.

If, in rare cases, the reconstituted solution shows any signs of fibril formation (viscous appearance) or insoluble matter, it should be discarded.

GlucaGen® HypoKit (glucagon):
Prior to reconstitution, the shelf life of the product is 3 years. GlucaGen® HypoKit should be stored at a temperature not exceeding 2-8°C. The User can store GlucaGen® HypoKit at a temperature not exceeding 25ºC for 18 months provided that the expiry date is not exceeded. The sealed container should be protected from light and freezing should be avoided.

The reconstituted GlucaGen® HypoKit should be used immediately after preparation. Any unused product or waste material should be disposed of in accordance with local requirements.

If, in rare cases, the reconstituted solution shows any signs of fibril formation (viscous appearance) or insoluble matter, it should be discarded.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: glucagon

Chemical name: His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

Molecular formula and molecular mass: $C_{153}H_{225}N_{43}O_{49}S$

Structural formula:

Physicochemical properties: Appearance: white or faintly coloured crystalline powder.

Product Characteristics

Glucagon 1 mg (1 IU) as hydrochloride.

Pharmaceutical standard: Ph. Eur. USP

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study demographics and trial design

One clinical study has been conducted to determine the pharmacokinetic and efficacy properties of GlucaGen®.

Study 2B was a randomized, open-labelled, 2-period cross over single-center study of GlucaGen® and glucagon injected intramuscularly in 38 healthy adult subjects

The following table shows a summary of the subject demographics for this study.

Table 5 - Summary of patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
2B	Open-label, randomized single dose, 2-way crossover	1 mg, i.m. 2 single doses separated by a 2-10 day wash out period	38	18-40 (26.3)	24M/14F

i.m.: intramuscular; M: male; F: female

14.2 Study Results

Clinical Efficacy measures and variables

Endpoints for bioequivalence for study 2B were AUC_{0-360}, C_{max} and T_{max} for glucagon and ratios of mean AUC_{0-360} and C_{max} between GlucaGen® and pancreatic glucagon to be completely within the bioequivalence limits of 80% to 125% at a 90% confidence interval. The primary efficacy endpoint for study 2A was AUC_{0-180}, C_{max}, and T_{max} for glucose.

Pharmacokinetic data showed similar glucagon concentrations over 6 hours with 90% confidence interval for ratios of GlucaGen®/Glucagon USP for AUC $_{0-360}$ and C_{max} within an 80% to 125% range. T_{max} was 13.2 minutes with GlucaGen® and 12.2 minutes with Glucagon USP which was considered an insignificant difference.

Table 6: Comparative Bioavailability Parameters of Glucagon Following a Single Dose

Glucagon (1 mg)				
Parameter	**Ratio GlucaGen® / Glucagon USP**	**p-value**	**Lower 90% Confidence interval**	**Upper 90% Confidence interval**
AUC_{0-360}	1.048	0.587	0.91	1.21
C_{max}	1.053	0.507	0.92	1.20
T_{max}	-	0.783		

Because of significant carry over effect, glucagon PK parameters for GlucaGen® and Glucagon USP were compared using only data from dosing day 1. Total number of subjects in this analysis was 37. Results from this study indicate that GlucaGen® and Glucagon USP are bioequivalent.

Study 2B showed plasma glucose level increase within 10 minutes following injection of GlucaGen® or Glucagon USP, reaching a maximal concentration of about 150 mg/dl in 30 minutes. The hyperglycaemic effects of the two treatments were essentially the same. Confidence intervals for ratio of GlucaGen®/Glucagon AUC and C_{max} were (0.98, 1.04) and (0.97, 1.03), respectively.

16 NON-CLINICAL TOXICOLOGY

Animal sourced glucagon was normally produced from extracted porcine and bovine pancreas although only genetically engineered (rDNA origin) formulations are now available. Glucagon (rDNA origin) is produced by fermentation using a yeast strain of *Saccharomyces Cerevisiae* as used in human insulin which is also recombinantly genetically engineered and contains the same plasmid expression except for the DNA-region encoding glucagon.

Acute Toxicity:

Glucagon, (rDNA origin), and pancreatic glucagon was administered i.v. to Wistar rats at varying doses of up to 100 mg/kg (Study 3). During observation, general signs of discomfort were seen shortly after dosing in treated groups including; decreased motor activity, hyperventilation and in coordination of movement. The LD_{50} values in each treated group were approximately 100 mg/kg.

In a single dose toxicity study, NMRI mice received i.v. varying doses of up to 200 mg/kg (Study 4). During observation, signs of general discomfort were noted shortly after dosing at the highest dose for both treated groups. Signs of general discomfort included decreased motor activity, ptosis, and decreased rectal temperature. The LD50 values for both treated groups were greater than 200 mg/kg.

In another study, Wistar rats were administered s.c. injections of glucagon (rDNA origin) at varying doses of up to 200 mg/kg or glucagon (pancreatic) at 200 mg/kg (Study 5). No significant toxicological findings were noted in the treatment groups.

Dosing rats with 200 mg/kg of either glucagon, (rDNA origin), or pancreatic glucagon resulted in body weight gain being adversely effected. No significant intergroup differences were noted between the two treatments. The LD_{50} was greater than 200 mg/kg body weight in both treatment groups and the no observed effect level was noted within the range of 50 to 200 mg/kg body weight.

See Table 6 for summary of acute toxicity studies.

Table 6: Acute Toxicity Studies

Study No.	Species/ Strain	Route of Admin.	No./Sex/Grp. (Total No.)	Dose (mg/kg)/ Duration	LD50 (mg/kg)	Conclusion

3	Rats/ Wistar	i.v.	5/sex/Grp. (60)	Glucagon,(rDNA origin): 0, 100, 33, 11 Pancreatic glucagon: 100 33. Single Dose	100	The i.v. LD50 values for rats of both Glucagon, (rDNA origin), and pancreatic glucagon was approximately 100 mg/kg. No difference between the Glucagon, (rDNA origin), and pancreatic glucagon
4	Mice/ NMRI	i.v.	5/sex/Grp. (60)	Glucagon, (rDNA origin): 0, 200, 50,12.5 Pancreatic glucagon: 200,50	->200	The i.v. LD50 values for mice of both Glucagon, (rDNA origin), and pancreatic glucagon was greater than 200 mg/kg.
5	Rat/ Wistar	s.c.	5/sex/Grp. (40)	Glucagon, (rDNA origin): 0, 50, 200 Pancreatic glucagon: 200 Single Dose	- >200 - no toxic effect level was between 50-200	The s.c. LD50 in rats was greater than 200 mg/kg . A no observed effect level was between the range of 50 to 200 mg/kg body weight

Chronic Toxicity:

Chronic toxicity studies of glucagon were conducted in Wistar and CD rats and beagle dogs for 28 days.

CD rats received glucagon, (rDNA origin), for four weeks by i.v. injection at varying doses of up to 5.0 mg/kg/day. Evidence of potential toxicity was seen in rats treated at 5.0 mg/kg/day. A clear no-toxic effect level was seen at a dosage of 1.0 mg/kg/day (Study 6).

In a 4-week study in Wistar rats, glucagon-(1-21)-peptide was administered i.v. at doses of 0.017, 0.665 or, 3.333 mg/kg/day (corresponding to 0.007, 0.271 and 1.353 µmol/kg/day) or glucagon 4.687 mg/kg/day (1.353 µmol/kg/day) daily (Study 7). No death or clinical signs of toxicity were noted. No macroscopic or histopathological changes related to treatment were found in rats receiving either glucagon-(1-21)-peptide or glucagon. Relative liver weights of rats receiving glucagon were significantly increased in comparison with rats receiving any

dosage of glucagon- (1-21)-peptide. Microscopic examination in the glucagon treated group revealed increased hepatic glycogen with statistical significance compared with rats given the high dose of glucagon- (1-21)-peptide.

In beagle dogs, i.v. doses of 1 or 5 mg/kg/day glucagon, (rDNA origin), or 5 mg/kg/day glucagon (pancreatic) were administered daily for 28 days (Study 8). No deaths occurred in these animals. Treated animals generally showed a higher incidence of soft and loose feces compared to controls with no apparent dose relationship.

No treatment-related differences were noted in body weight gain, food consumption, ocular changes, hematological parameters, or urine parameters between the treated and the control groups. Treatment related effects included minor clinical signs, increased plasma glucose levels and heart rate immediately after dosing.

See Table 7 for summary of chronic toxicity studies.

Published literature highlights glucagon to be almost devoid of toxic effects in rabbits, cats and dog.

Table 7: Chronic Toxicity Studies

Study No.	Species/ Strain	Route of Admin.	No./Sex/ Grp. (Total No.)	Dose (mg/kg)/day Duration	LD50 (mg/kg)	Conclusion
6	Rats/ CD	i.v.	10/sex/Grp. (80)	Glucagon, (rDNA origin): 0, 0.2, 1.0, 5.0 4 weeks	- no toxic effect level seen at 1.0	-No mortality - Potential toxicity was seen at 5.0 mg/kg/day dosing

Study No.	Species/ Strain	Route of Admin.	No./Sex/ Grp. (Total No.)	Dose (mg/kg)/day Duration	LD50 (mg/kg)	Conclusion
7	Rats/ Wistar	i.v.	10/sex/Grp. (100)	Glucagon-(1-21) -peptide: 0, 0.017, 0.665, 3.333 Glucagon: 4.687 28 Days	-	- No mortality - Intravenous administration of Glucagon-(1-21)-peptide at determined doses were well tolerated
8	Dog/ Beagle	i.v.	3/sex/Grp. (24)	Glucagon, (rDNA origin): 0, 1.0, 5.0 Pancreatic glucagon: 5.0 28 days	-	- No mortality - Increase in heart rate in the 5 mg/kg/day Glucagon (ge) and Glucagon (Novo) groups after dose administration in Weeks 1 and 4

Carcinogenicity:

The treatment schedule of glucagon, (rDNA origin)**,** for short-term use does not indicate the need for animal testing for oncogenic/carcinogenic potential and therefore, indications from the chemical characterization of glucagon, (rDNA origin), should not differ from the animal sourced glucagon.

Mutagenicity:

The genotoxic potential of glucagon was assessed in a series of recognized in vitro and in vivo assays for mutagenic-genotoxic activity.

The mutagenic potential of glucagon was investigated using *Salmonella typhimurium* strains of TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 uvrA- tester strain in the absence and presence of a S-9 metabolic activation system (rat liver post-mitochondrial preparation) (Study 9). Negative and positive control treatments for all tester strains were observed to be in acceptable ranges and significantly elevated by positive control treatments. All five tester

strains with both formulations did not reproducibly induce significant increases in the number of revertants when tested up to 5000 µg/plate in the absence or presence of the metabolic activating system. Based on the experimental conditions, it was shown that weak mutagenic activity was observed in the presence of added metabolic activation system.

The cytogenetic potential of glucagon was investigated *in vitro* using human lymphocytes in the absence or presence of an S-9 metabolic activation system (rat liver post-mitochondrial preparation) (Study 10). At very high doses (1056 µg/mL and 2500 µg/mL), glucagon, (rDNA origin)**,** was observed to have a small effect on the ability to induce polyploidy and structural chromosome aberrations in human lymphocytes in the absence of a S-9 metabolic activation system.

See Tables 8 and 9 for *in vitro* and *in vivo* mutagenicity studies.

Table 8: In vitro Mutagenicity Studies:

Study No.	**Bacterial Strain/ Test System**	**Metabolizing System**	**Received Final Concentration**	**Contact/ Incubation Time**	**Positive Control**	**Results**
9	*S. typhimurium* (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA-)	Studies A and B conducted in absence or presence of S-9 mix S-9mix: Aroclor 1254 induced rat liver post-mitochondrial fraction (500 mg/kg)	8-5000 µg/plate in DMSO	Incubation time = 72 hours	TA98 = 2NF TA100/ TA1535 = NaN3 TA1537 = AAC WP2 uvrA-= NQO AII = AAN	- Weak mutagenic activity with both forms of glucagon in all 5 tester strains in presence of S-9 mix

10	Human lymphocytes	Studies A and B conducted in absence or presence of S-9 mixS-9mix: Aroclor 1254 induced rat liver post-mitochondrial fraction (500 mg/kg)	446-2500 mg/plate in DMSO	Incubation time = 72 or 96 hours	MMS CPA	Induce structural chromosome aberrations in human lymphocytes in absence of S-9 at very high doses. No aberrations noted in presence of S-9

2NF = 2-nitroflurane; NaN3 = sodium azide; AAC = 9-aminoacridine; NQO = 4-nitroquinoline-1-oxide; AAN = 2-aminoanthracen; MMS = methyl methanesulphonate; CPA = cyclophosphamide

Mouse bone marrow micronucleus tests were assayed *in vivo* using varying i.v. doses of up to 200 mg/kg of either glucagon,(rDNA origin), or glucagon (pancreatic) in two separate experiments (Study 11). Cyclophosphamide (CPA) 40 mg/kg i.v. injection was used as a positive control with positive control animals exhibiting an increase in the number of micronucleated polychromatic erythrocytes (PCE) as compared to that of the control groups. Both glucagon preparations induced micronuclei in polychromatic erythrocytes of the bone marrow in the male mice.

Table 9: In vivo Mutagenicity Studies:

Study No	Species / Strain	No./Sex/ Grp. (Total No.)	Route of Admin.	Doses (mg/kg)/ Duration	Controls	Experimental Conditions	Results

11	Mouse/ CD-1	15/sex/Grp. CPA 5/sex/Grp. (130) 15/sex/Grp. CPA: 5/sex/Grp. (130)	i.v.	Glucagon, (rDNA origin): 0, 50, 100, 200, CPA: 40 Pancreatic glucagon: 0, 50, 100, 200 Glucagon (rDNA origin): 200CPA: 40 Single Dose	Positive: CPA Negative: 0.01N HCl	Test chemical and vehicle treated mice sacrificed after 24, 48, 72 hours; CPA mice sacrificed after 24 hours.	Both forms of glucagon induced micronuclei in polychromatic erythrocytes of the bone marrow in male mice

CPA = cyclophosphamide

Reproduction and Teratology:

Animal reproduction studies have not been conducted with GlucaGen®. Studies in rats have shown that glucagon does not cause impaired fertility.

Glucagon, (rDNA origin)**,** was administered to pregnant rats as single intravenous doses of 0 (control), 0.4, 2.0, and 10.0 mg/kg daily on Days 7 -17 of gestation (Study 12). Mother animals who were administered 10.0 mg/kg exhibited an inhibition of weight gain and showed signs of toxicity such as yolk sac tumour and mastadenoma, transient tachypnea, arterial thrombosis and abnormal respiration. The majority of these observations were not considered to be related to drug administration.

In a second teratogenicity study, albino rabbits were administered glucagon, (rDNA origin)**,** at doses of 0 (control), 0.4, 2.0, and 10.0 mg/kg as a once daily i.v. dose on Days 6-18 of gestation (Study 13).

The 10.0 mg/kg dose administered aggravated the general conditions in mother animals as noted by a decrease in spontaneous movement and tachypnea. These pharmacological effects were observed in a few cases and animals recovered within a few minutes. In animals that did not recover, their conditions progressed to death.

Under the experimental conditions, a 10 mg/kg dose is considered to be the maximum dose to have no toxic or teratogenic effects on fetal development. A 2.0 mg/kg dose is considered the maximum dose at which no effects on the mother animal was noted.

See Table 10 for Reproduction and Teratology Studies.

Table 10: Reproduction and Teratology Studies

Study No.	Species/ Strain	Route of Admin.	No./Sex/Grp. (Total No.)	Dose (mg/kg)/ Duration	Conclusion
12	Rats/SD	i.v.	34/Females/ Grp. (136)	Glucagon, (rDNA origin): 0, 0.4, 2.0, 10. On Days 7-17 of gestation.	-Mother animals were noted to have inhibition of weight gain -In the 10mg/kg group, toxic signs were noted in mother animals and not in fetuses.
13	Rabbits/ albino SPF	i.v.	16/Females/ Grp. (64)	Glucagon, (rDNA origin): 0, 0.4, 2.0, 10.0 On Days 6-18 of gestation.	-Dose of 10 mg/kg aggravated the general condition of the mother animal and induced death but no teratogenic effects in fetuses were noted.

Local Tolerance:
A study was conducted in New Zealand White rabbits using single 1 mg doses of glucagon (rDNA) or glucagon i.m (Study 14). Results showed that both glucagon preparations did not cause toxic reactions. See Table 11.

Table 11: Local Tolerance Toxicity

Study No.	Species/ Strain	Route of Admin.	No./Sex/Grp. (Total No.)	Doses (mg/kg)/ Duration	Observations
14	Rabbits/ New Zealand	i.m.	6/Females/Grp. (18)	Glucagon, (rDNA origin): 1 Pancreatic glucagon: 1 Positive control acetic acid 0.75% Control (injection site contralateral to treatment site): Sterile isotonic saline Single Dose	- No abnormalities were found 8 days after dosing upon macroscopic examination.

Antigenicity:
In antigenicity studies, rabbits (Study 15, 16) and guinea pigs (Study 17, 18) were administered GlucaGen®, (rDNA origin)**,** or glucagon i.m, s.c, or i.v at doses ranging from 0.02 mg/kg to 12.5 mg/kg, respectively. Active anaphylactic response was detected in both glucagon preparations with glucagon, (rDNA origin)**,** being no more antigenic than glucagon. Low levels of anaphylactic antibodies were detected in both test compounds with no differences between the two compounds.

See Table 12 for antigenicity studies.

Table 12: Antigenicity studies

Study No.	Species/ Strain	Route of Admin.	No./Sex/Grp. (Total No.)	Dose / Duration	Observations

15	Rabbit Strain: N/A	i.m.	10/Males/Grp. (40)	Glucagon, (rDNA origin): 1 mg/rabbit Glucagon: 1 mg/rabbit	Rabbit responses to master lot, crystals of intermediate purity were not significantly different, whereas response to crude GlucaGen® differed from the other groups. A SCP-content of 200 ppm does not provoke antibody formation in rabbits.
16	Rabbits/ New Zealand	s.c.	Preliminary Study:2/Males/Grp. (20)	Glucagon, (rDNA origin): 0.02, 0.2,2.0, 6.25 mg/kg Glucagon: 0.02, 0.2,2.0, 6.25 mg/kg Positive control: BSA 4 mg/kg 3 injections a week apart	- Low titre levels of specific antibody were induced by both glucagon formulations. - Glucagon (rDNA) was no more effective in inducing specific hemagglutination antibodies than pancreatic glucagon.
			Main Study:5/Males/ Grp.(40)	Glucagon,(rDNA origin): 0.02, 2.0, 12.5 mg/kg Glucagon: 0.02, 2.0, 12.5 mg/kg Positive control: BSA 4 mg/kg Negative control: Saline 3 injections a week apart	

BSA = Bovine serum albumin; N/A: Not available

Table 12: Antigenicity studies (Continued)

Study No.	Species/ Strain	Route of Admin.	No./Sex/Grp.(Total No.)	Dose (mg/kg)/ Duration	Observations
17	Guinea pig/Dunkin -Hartley	s.c.i.v.	Preliminary Study: 2/Males/Grp. (Total 22)	Glucagon, (rDNA origin): 0.02, 0.2, 2.0, 6.25 Glucagon: 0.02, 0.2, 2.0, 6.25 Positive control: BSA: 1 Negative control: Saline 2 injections a week apart	- Mortality was observed following the i.v. challenge injection -Active anaphylactic response was detected in both formulations but Glucagon, (rDNA origin), was no more antigenic than Glucagon.
			Main Study: 4/Males/Grp. and 2/Males/Grp. (Total 32)	Glucagon, (rDNA origin): 2.0, 6.25, 12.5 Glucagon: 2.0, 6.25, 12.5 Positive control: BSA: 1 Negative control: Saline	
18	Guinea pig/Dunkin -Hartley	s.c.i.v.	Preliminary Study: 2/Males/Grp. (Total 20)	Glucagon, (rDNA origin): 0.02, 0.2, 2.0, 6.25 Glucagon: 0.02, 0.2, 2.0, 6.25 Positive control BSA: 1 Negative control: Saline 2 injections a week apart	-Low levels of specific anaphylactic antibodies were detected in both formulations - The response to Glucagon, (rDNA origin), **was** no greater than that to glucagon.

			Main Study: 3/Males/Grp (Total 24)	Glucagon, (rDNA origin): 2.0, 6.25, 12.5 Glucagon: 2.0, 6.25, 12.5 Positive control: BSA 1 Negative control: Saline 2 injections a week apart	

BSA = Bovine serum albumin; N/A: Not available

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

GlucaGen® 1 mg

GlucaGen® HypoKit 1 mg

Glucagon

Read this carefully before you start taking **GlucaGen®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **GlucaGen®.**

Serious Warnings and Precautions

After intramuscular injection the patient will normally respond within 10 minutes. If they do not respond within 10 minutes, medical attention should be sought immediately; 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 the liver glycogen and prevent relapse of hypoglycemia.

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

What is GlucaGen® used for?

GlucaGen® is used to treat severe hypoglycemic reactions (unconsciousness due to low blood sugar), which may occur if you are a person with insulin treated diabetes.

How does GlucaGen® work?

GlucaGen® is a high blood sugar agent that helps to release the glycogen in the liver to the blood as glucose.

Early symptoms of hypoglycemia may include:

- sweating
- drowsiness
- dizziness

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

If not treated early, hypoglycemia may worsen and the person may have severe hypoglycemia.

Signs of severe hypoglycemia include:

- confusion
- unconsciousness
- seizures
- death

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, GlucaGen® 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 GlucaGen® 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*.

What are the ingredients in GlucaGen®?

Medicinal ingredients: Glucagon 1 mg (1 IU) as hydrochloride.

Non-medicinal ingredients: Lactose monohydrate, hydrochloric acid and/or sodium hydroxide (pH adjusters) and water for injection.

GlucaGen® comes in the following dosage forms:

Powder (compacted) and solvent for solution for injection. After reconstitution the solution contains glucagon 1 mg/ mL.

Do not use GlucaGen® if:

- You are allergic or hypersensitive to glucagon or if you have an adrenal gland tumour.

Due to the instability of GlucaGen® in solution, the product should be used immediately after reconstitution and must not be given as an intravenous infusion.

GlucaGen® should be given only if the patient is unconscious or unresponsive and unable to ingest oral glucose.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GlucaGen®. Talk about any health conditions or problems you may have, including if you:

- Are fasting, or have low levels of adrenaline, chronic low blood sugar or low blood sugar caused by drinking too much alcohol.
- Have chronic hypoglycemia.
- Have an adrenal gland tumour.
- Have a tumour that releases glucagon or insulin.
- Are allergic to glucagon or lactose or components of the container.
- Are pregnant or breast feeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Discard any unused portion.

The following may interact with GlucaGen®:

- insulin
- indomethacin
- warfarin
- beta-blockers

How to take GlucaGen®:
What to tell your friends, family, carer or co-workers

Your doctor may have given you GlucaGen® 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 GlucaGen® and where it is** kept before an emergency arises.
- **They must inject** GlucaGen® into a muscle. Mix the GlucaGen® powder and solvent just before giving the injection into the muscle and follow the instructions given in the section below.
- **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 GlucaGen® depletes glycogen stores. The high sugar snack will prevent relapse of the hypoglycemia.
- The unconscious person should be on their side to prevent choking.

After using GlucaGen®, 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.

Usual dose:

- **Adults:** inject 1 mL
  (GlucaGen® HypoKit: marked as 1/1 on the syringe).

- **Children above 25 kg** or older than 6 to 8 years: inject 1mL
  (GlucaGen® HypoKit: marked as 1/1 on the syringe).

- **Children below 25 kg** or younger than 6 to 8 years: inject ½ mL
  (GlucaGen® HypoKit: marked as 1/2 on the syringe).

Doses must be given by intramuscular injection.

Overdose:

If you have been given too much GlucaGen® it may cause nausea and vomiting. Specific treatment is not usually necessary.

If you think you, or a person you are caring for, have taken too much GlucaGen®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

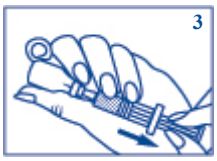
Not applicable.

Reconstitution

GlucaGen® HypoKit:

1. Remove the plastic cap from the vial. Pull the needle cover off the syringe. Do not remove the plastic back-stop from the syringe. Insert the needle through the rubber stopper (within the marked circle) of the vial containing GlucaGen® and inject all the liquid from the syringe into the vial.

2. Without taking the needle out of the vial, gently shake the vial until GlucaGen® has completely dissolved, and the solution is clear.



3. Make sure the plunger is completely down. While keeping the needle in the liquid, slowly withdraw all the solution back into the syringe. Do not pull the plunger out of the syringe.

   It is important to remove any air bubbles from the syringe as follows:
   - With the needle pointing upwards, tap the syringe with your finger
   - Push the plunger slightly to release any air that has collected at the top of the syringe.

   Continue to push the plunger until you have the correct dose for injection (For how much to use, see *How to take GlucaGen®*). A small amount of liquid will be pushed out when you do this.

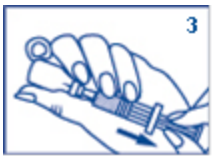
4. Inject the dose into a muscle.

Do not attempt to put the cap back on the needle of the used syringe. Place the used syringe in the orange box and dispose the used needle in a sharps container at the next available opportunity.

GlucaGen®:

1. Remove both of the plastic caps from the vials. Draw up all the water into a disposable syringe. Insert the needle through the rubber stopper (within the marked circle) of the vial containing GlucaGen® and inject all the water from the syringe into the vial.

2. Without taking the needle out of the vial, gently shake the vial until GlucaGen® has completely dissolved, and the solution is clear.



3. Make sure the plunger is completely down. While keeping the needle in the liquid, slowly withdraw all the solution back into the syringe. Do not pull the plunger out of the syringe.

   It is important to remove any air bubbles from the syringe as follows:
   - With the needle pointing upwards, tap the syringe with your finger.
   - Push the plunger slightly to release any air that has collected at the top of the syringe.

   Continue to push the plunger until you have the correct dose for injection (For how much to use, see *Usual dose*). A small amount of liquid will be pushed out when you do this.

4. Inject the dose into a muscle.

What are possible side effects from using GlucaGen®?

These are not all the possible side effects you may feel when taking GlucaGen®. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, GlucaGen® (glucagon) can have side effects. The most common side effects are nausea and dizziness.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON (less than 1 in 10)	√		

Nausea: feeling sick			
UNCOMMON (less than 1 in 100) Vomiting	√		
RARE (less than 1 in 1,000) Stomach: abdominal pain	√		
VERY RARE (less than 1 in 10,000) Allergic reaction: wheezing, sweating, rapid heart beat, rash, swollen face), collapse (anaphylactic reaction)		√ (get medical help immediately)	
UNKNOWN (we do not know how often these may happen) Skin problems where the injection is given	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2°C and 8°C (refrigerator). The User can also store GlucaGen® HypoKit outside refrigerator at temperature not exceeding 25ºC for 18 months provided that the expiry date is not exceeded.

Do not freeze to prevent damage to the product.

Store in the original package to protect from light.

Use immediately after preparation - do not store for later use.

Do not use if the solution in rare cases looks like a gel or if any of the powder has not dissolved properly.

Do not use if the plastic cap(s) is/are loose or missing when you receive the product - return the product to your local pharmacy.

Keep out of reach and sight of children.

If you want more information about GlucaGen®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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