Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

GlucaGen HypoKit 1 mg powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Human glucagon produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

One vial contains 1 mg glucagon as hydrochloride corresponding to 1 mg (1 IU) glucagon/ml after reconstitution.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapeutic indication
GlucaGen is indicated for treatment of severe hypoglycaemic reactions, which may occur in the management of insulin treated children and adults with diabetes mellitus.

Diagnostic indication
GlucaGen is indicated for motility inhibition in examinations of the gastrointestinal tract in adults.

4.2 Posology and method of administration

Posology

- *Therapeutic indication (Severe hypoglycaemia)*

Dosage for adult patients: Administer 1 mg by subcutaneous or intramuscular injection.

Special populations
Paediatric population (< 18 years old): GlucaGen can be used for the treatment of severe hypoglycaemia in children and adolescents.

Dosage for paediatric patients: Administer 0.5 mg (children below 25 kg or younger than 6–8 years) or 1 mg (children above 25 kg or older than 6–8 years).

Elderly (≥ 65 years old): GlucaGen can be used in elderly patients.

Renal and hepatic impairment: GlucaGen can be used in patients with renal and hepatic impairment.

- *Diagnostic indication (Inhibition of gastrointestinal motility)*

Dosage for adult patients: The diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum and small bowel is 0.2–0.5 mg given as intravenous injection or 1 mg given intramuscularly; the dose to relax the colon is 0.5–0.75 mg intravenously or 1–2 mg intramuscularly.

Special populations
Paediatric population (< 18 years old): The safety and efficacy of GlucaGen for inhibition of gastrointestinal motility in children and adolescents have not been established. No data are available.
Elderly (≥ 65 years old): GlucaGen can be used in elderly patients.

Renal and hepatic impairment: GlucaGen can be used in patients with renal and hepatic impairment.

Method of administration
Dissolve the compacted powder in the accompanying solvent, as described in section 6.6.

Therapeutic indication (Severe hypoglycaemia):
Administer by subcutaneous or 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 hypoglycaemia. If the patient does not respond within 10 minutes, intravenous glucose should be given.

Diagnostic indication (Inhibition of gastrointestinal motility):
GlucaGen must be administered by medical personnel. Onset of action after an intravenous injection of 0.2–0.5 mg occurs within one minute and the duration of effect is between 5 and 20 minutes. The onset of action after an intramuscular injection of 1–2 mg occurs after 5–15 minutes and lasts approximately 10–40 minutes.

After end of the diagnostic procedure oral carbohydrate should be given, if this is compatible with the diagnostic procedure applied.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Phaeocromocytoma

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Therapeutic indication

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

Glucagon will not be effective in patients whose liver glycogen is depleted. For that reason, glucagon has little or no effect when the patient has been fasting for a prolonged period, or is suffering from adrenal insufficiency, chronic hypoglycaemia or alcohol induced hypoglycaemia.

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.

Diagnostic indication

Persons who have been given glucagon in connection with diagnostic procedures may experience discomfort, in particular if they have been fasting. Nausea, hypoglycaemia, and blood pressure changes have been reported in these situations. After the end of a diagnostic procedure, oral carbohydrates should be given to patients who have been fasting, if this is compatible with the diagnostic procedure applied. If fasting is needed post-examination or in case of severe hypoglycaemia, glucose given intravenously may be required.

GlucaGen may increase myocardial oxygen demand, blood pressure, and pulse rate. Monitor patients with cardiac disease during use of GlucaGen as a diagnostic aid and treat if indicated.

GlucaGen may cause short term hyperglycaemia in patients with diabetes mellitus when used as a diagnostic aid. Monitor patients with diabetes for changes in blood glucose levels during use and treat if indicated.

Caution should be observed in patients with glucagonoma when used as diagnostic aid.

Therapeutic and diagnostic indications

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

Glucagon stimulates the release of catecholamines. In the presence of phaeocromocytoma, glucagon can cause the tumour to release large amounts of catecholamines, which will cause an acute hypertensive reaction. Glucagon is contraindicated in patients with phaeochromocytoma (see section 4.3).

Excipients

GlucaGen contains less than 1 mmol sodium (23 mg) per maximum dose (2 ml), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Insulin: Reacts antagonistically towards glucagon.

Indomethacin: Glucagon may lose its ability to raise blood glucose or paradoxically may even produce hypoglycaemia.

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.

Interactions between GlucaGen and other drugs are not known when GlucaGen is used in the approved indications.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 unborn and the neonate. GlucaGen can be used during pregnancy.

Breast-feeding
Glucagon is cleared from the bloodstream very fast (mainly by the liver) ($t_{1/2}$= 3–6 min.); thus the amount excreted in the milk of nursing mothers following treatment of severe hypoglycaemic reactions is expected to 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. GlucaGen can be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

After a severe hypoglycaemic event, the patient's ability to concentrate and react may be impaired. Therefore the patient should not drive or operate machinery after a severe hypoglycaemic event until the patient has stabilised.

After diagnostic procedures hypoglycaemia has been reported infrequently. Therefore driving a vehicle and operating machinery should be avoided until the patient has had a meal with oral carbohydrates.

4.8 Undesirable effects

Summary of the safety profile

Severe adverse reactions are very rare, although nausea, vomiting and abdominal pain may occur occasionally. Hypersensitivity reactions, including anaphylactic reactions, have been reported as 'very rare' (less than 1 case per 10,000 patients). When used in the diagnostic indication, hypoglycaemia/hypoglycaemic coma have been reported, especially in patients who have fasted. Cardiovascular adverse events, such as tachycardia and blood pressure changes have only been reported when GlucaGen is used as an adjunct in endoscopic or radiographic procedures.

Tabulated summary of adverse reactions

Frequencies of undesirable effects considered related to treatment with GlucaGen during clinical trials and/or post-marketing surveillance are 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.

Therapeutic indication

System Organ Class	**Subject incidence**	**Adverse drug reaction**
Immune system disorders	Very rare < 1/10,000	Hypersensitivity reactions including anaphylactic reaction/shock
Gastrointestinal disorders	Common ≥ 1/100 to < 1/10 Uncommon ≥ 1/1,000 to < 1/100 Rare ≥ 1/10,000 to < 1/1,000	Nausea Vomiting Abdominal pain
General disorders and administration site conditions	Not known (cannot be estimated from the available data)	Injection site reactions

Paediatric population

Based on data from clinical trials and post-marketing experience, the frequency, type and severity of adverse reactions observed in children are expected to be the same as in adults.

Other special populations

Based on data from clinical trials and post-marketing experience, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment are expected to be the same as in the general population.

Diagnostic indication

System Organ Class	**Subject incidence**	**Adverse drug reaction**
Immune system disorders	Very rare < 1/10,000	Hypersensitivity reactions including anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon ≥ 1/1,000 to < 1/100 Very rare < 1/10,000	Hypoglycaemia*[1] Hypoglycaemic coma
Cardiac disorders	Very rare < 1/10,000	Tachycardia*[2]
Vascular disorders	Very rare < 1/10,000 Very rare < 1/10,000	Hypotension*[2] Hypertension*[2]
Gastrointestinal disorders	Common ≥ 1/100 to < 1/10 Uncommon ≥ 1/1,000 to < 1/100 Rare ≥ 1/10,000 to < 1/1,000	Nausea Vomiting Abdominal pain
General disorders and administration site conditions	Not known (cannot be estimated from the available data)	Injection site reactions

*[1] After a diagnostic procedure this could be more pronounced in patients that have fasted (see section 4.4).

*[2] Cardiovascular adverse events have only been reported when GlucaGen is used as an adjunct in endoscopic or radiographic procedures.

Paediatric population

There are no data available on the diagnostic use of GlucaGen in children.

Other special populations

Based on data from clinical trials and post-marketing experience, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment are expected to be the same as in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the case of overdose, the patient may experience nausea and vomiting. Due to the short half life of glucagon, these symptoms will be transient.

In case of dosages substantially above the approved range, the serum potassium may decrease and should be monitored and corrected, if needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pancreatic hormones, Glycogenolytic hormones: H04AA01.

Mechanism of action
Glucagon is a hyperglycaemic agent that mobilises hepatic glycogen, which is released into the blood as glucose. Glucagon inhibits the tone and motility of the smooth muscle in the gastrointestinal tract.

Pharmacodynamic effects
When used in treatment of severe hypoglycaemia, an effect on blood glucose is usually seen within 10 minutes.

The onset of inhibitory effect on gastrointestinal motility occurs within 1 minute after an intravenous injection. Duration of action is in the range 5–20 minutes depending on the dose. The onset of effect occurs within 5–15 minutes after an intramuscular injection, with a duration of 10–40 minutes.

5.2 Pharmacokinetic properties

Metabolism
Glucagon 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
Glucagon has a short half-life in the blood of about 3–6 minutes. Metabolic clearance rate of glucagon in humans is approximately 10 ml/kg/min.

5.3 Preclinical safety data

No relevant pre-clinical data exist that provide information useful to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydrochloric acid for pH adjustment
Sodium hydroxide for pH adjustment
Water for injections

The reconstituted solution contains glucagon 1 mg/ml and lactose monohydrate 107 mg/ml.

6.2 Incompatibilities

There are no known incompatibilities with GlucaGen.

6.3 Shelf life

Prior to reconstitution, the shelf life of the product is 36 months.

The reconstituted GlucaGen should be used immediately after preparation.

6.4 Special precautions for storage

Do not freeze.

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

GlucaGen HypoKit should be stored at a temperature of 2-8°C (in a refrigerator). The user can store GlucaGen HypoKit at a temperature not exceeding 25ºC for 18 months provided that the expiry date is not exceeded. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Container for GlucaGen:

Vial made of glass type I, Ph. Eur., closed with a bromobutyl stopper and covered with an aluminium cap.

Containers for solvent:
Vial made of glass type I, Ph. Eur., closed with a bromobutyl disc with teflon and covered with an aluminium cap
or
pre-filled syringe made of glass type I, Ph. Eur., with plunger (bromobutyl rubber) and needle.

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

Not all presentations of GlucaGen may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution
Inject the water for injections (1.1 ml) into the vial containing the glucagon compacted powder. Shake the vial gently until the glucagon is completely dissolved and the solution is clear. Withdraw the solution back into the syringe.
Note that a syringe with a thinner needle and a finer graduation may be more suitable for use in diagnostic procedures.

The reconstituted solution appears clear and colourless and forms an injection of 1 mg (1 IU) per ml to be administered subcutaneously, intramuscularly or intravenously (injection).

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

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880
Bagsvaerd
Denmark

8 MARKETING AUTHORISATION NUMBER

PA0218/031/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 1991

Date of last renewal: 15October 2006

10 DATE OF REVISION OF THE TEXT

February 2023