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

Treatment of severe hypoglycaemic reactions, which may occur in the management of insulin treated persons with diabetes.

4.2 Posology and method of administration

Posology

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.

Method of administration

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

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.

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 of the administered product should be clearly recorded. It is reccomended to record the batch umber as well.

Due to the instability of GlucaGen in solution, the product should be given immediately after reconstitution.

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.

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.

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).

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.

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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov

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.

Pharmacodynamic effects

When used in treatment of severe hypoglycaemia, an effect on blood glucose is usually seen within 10 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 monohydrateHydrochloric 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

GlucaGen HypoKit 1 mg:
The expiry date of the product is indicated on the packaging materials

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 1 mg:
The user can store GlucaGen HypoKit at a temperature below 25ºC 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:

Pre-filled syringe made of glass type I, Ph. Eur., with plunger (bromobutyl rubber) and needle.

The vial is 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

Reconstitution

GlucaGen HypoKit 1 mg:
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.

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

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

7. REGISTRATION HOLDER:

Novo Nordisk Ltd.
1 Atir Yeda St.,
Kfar-Saba 4464301, Israel

8. MANUFACTURER

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

9. REGISTRATION NUMBER:

GlucaGen HypoKit 1 mg: 102-38-28662

Revised in March 2023 according to MoH guidelines