**AUSTRALIAN PRODUCT INFORMATION**

**GlucaGen® HypoKit® glucagon hydrochloride**

## 1. NAME OF THE MEDICINE

Glucagon hydrochloride

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glucagon is a polypeptide hormone consisting of 29 amino acids in a single chain. Glucagon hydrochloride is synthesised by genetic engineering from yeast (Saccharomyces cerevisiae) and has the same amino acid sequence as natural human glucagon.

GlucaGen HypoKit contains glucagon hydrochloride. The reconstituted solution contains glucagon 1 mg/mL and lactose monohydrate 107 mg/mL.

## 3. PHARMACEUTICAL FORM

GlucaGen HypoKit is powder and solvent for solution for injection. The powder may appear more like a powdery tablet upon settling.

Before reconstitution the powder should be a white or nearly white powder (which may appear more like a powdery tablet upon settling). The solvent should be clear and colourless without particles. 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.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Therapeutic

- Treatment of severe hypoglycaemic reactions which may occur in the management of diabetic patients receiving insulin or oral hypoglycaemic agents.

To prevent the occurrence of secondary hypoglycaemia, oral carbohydrate should be given to restore the hepatic glycogen when the patient has responded to the treatment.

The mechanism and hence treatment of sulfonylurea-induced hypoglycaemia differs from that of severe insulin-induced hypoglycaemia in some important ways. Consciousness should preferably be restored by the administration of intravenous glucose. If glucagon is used due to the unavailability of intravenous glucose (e.g. before reaching a hospital) care should be taken to protect against secondary hypoglycaemia with constant monitoring of the patient's blood sugar level by medical personnel. Subsequent administration of intravenous glucose may be required.

Diagnostic

- Motility inhibitor in examinations of the gastrointestinal tract in adults, e.g. double contrast radiography and endoscopy.

## 4.2 Dose and Method of Administration

Dosage

**Severe Hypoglycaemia**

For adults and children above 25 kg, the full dose (corresponding to 1 mg glucagon) should be injected. For children below 25 kg, inject half the amount (corresponding to 0.5 mg).

**Diagnostic Indications**

Doses range from 0.2 to 2 mg depending on the diagnostic technique used and the route of administration. The usual diagnostic dose for relaxation of the stomach, duodenal bulb, duodenum and small bowel is 0.2-0.5 mg given intravenously or 1 mg given intramuscularly. The usual dose to relax the colon is 0.5-0.75 mg intravenously or 1-2 mg intramuscularly.

Method of Administration

The freeze dried glucagon should be dissolved in the accompanying diluent. Inject the water for injections (1.1 mL) into the vial containing the freeze-dried glucagon. Gently shake the vial until the glucagon is completely dissolved and the solution is clear. Withdraw the solution back into the syringe.

**Severe Hypoglycaemia**

*Administration by medical persons*

Administer 0.5 to 1 mg of glucagon by subcutaneous, intramuscular or intravenous injection. The patient will normally respond within 10 minutes. When the patient has responded to treatment, give oral carbohydrate to restore the liver glycogen and to prevent secondary hypoglycaemia. If the patient does not respond within 10 minutes, intravenous glucose should be given.

*Administration by non-medical persons*

Administer 0.5 to 1 mg of glucagon by subcutaneous or intramuscular injection into the thigh or buttocks or upper arm. The patient will normally respond within 10 minutes to the glucagon injection, and oral carbohydrate should be given to restore liver glycogen and to prevent secondary hypoglycaemia. *Medical assistance must be sought for all unconscious patients.* Always notify the physician if glucagon has been used, as an adjustment in anti-diabetic therapy may be required.

**Diagnostic Indications**

Note that a syringe with a thinner needle and a finer graduation than that supplied in GlucaGen HypoKit may be more suitable for use in diagnostic procedures.

*Inhibition of gastrointestinal motility*

GlucaGen HypoKit must be administered by medical persons. 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 depending on the organ under examination. The onset of action after an intramuscular injection of 1–2 mg occurs after 5-15 minutes, lasting for 10-40 minutes depending on the organ.

At the end of the diagnostic procedure oral carbohydrate should be given to patients who have been fasting, assuming this is compatible with the diagnostic procedure performed.

## 4.3 Contraindications

- Phaeochromocytoma (glucagon can provoke a release of catecholamine resulting in sudden and severe hypertension)
- Insulinoma (after an initial rise in blood glucose, hypoglycaemia may be exacerbated by glucagon-induced insulin secretion)
- Glucagonoma
- Hypersensitivity to glucagon or any of the excipients

## 4.4 Special Warnings and Precautions for Use

Hepatic glycogen is required for glucagon to be of benefit in hypoglycaemia. Glucagon will have little or no effect when the patient is fasting or is suffering from adrenal insufficiency, chronic hypoglycaemia or alcohol induced hypoglycaemia.

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, assuming this is compatible with the diagnostic procedure applied. If fasting is needed post-examination or in case of severe hypoglycaemia, intravenous glucose may be required.

It should be borne in mind that glucagon is an insulin antagonist. Caution should be observed with regard to rebound hypoglycaemia if glucagon is used in patients with insulinoma (after an initial rise in blood glucose, hypoglycaemia may be exacerbated by glucagon-induced insulin secretion) or glucagonoma.

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.

Due to the instability of GlucaGen in solution, GlucaGen HypoKit should be used immediately after reconstitution and must not be administered by intravenous ***infusion***.

No studies on the effects on the ability to drive and use machines have been performed. After diagnostic procedures, hypoglycaemia has been reported infrequently. Therefore driving a vehicle should be avoided until the patient has had a meal with oral carbohydrates.

Use in elderly
No data available.

Paediatric use
GlucaGen can be used for the treatment of severe hypoglycaemia in children and adolescents.

The safety and efficacy of GlucaGen for inhibition of gastrointestinal motility in children and adolescents have not been established. No data are available.

Effects on laboratory tests
No data available.

## 4.5 Interaction with Other Medicines and Other Form of Interactions

Glucagon may potentiate the anticoagulant activity of warfarin when administered at supra-physiological doses much greater than that required for treatment of hypoglycaemia.

Glucagon has a positive inotropic action which can reverse the cardiovascular depression of profound β blockade. Patients taking beta-blockers might be expected to have a greater increase in both pulse and blood pressure, which might be expected to be temporary due to glucagon's short half life. The increase in blood pressure and pulse rate may require therapy in patients with coronary artery disease.

Insulin: Reacts antagonistically towards glucagon.

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

## 4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No data available.

Use in pregnancy
Reproduction studies have not been performed in animals. Glucagon does not cross the human placental 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.

Use in lactation
Glucagon is cleared from the bloodstream very quickly (mainly by the liver; t½ = 3-6 min); therefore, the amount excreted within the milk of nursing mothers after conventional treatment (1 mg on rare occasions) 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.

## 4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 Adverse Effects (Undesirable Effects)

Frequencies of undesirable effects considered related to GlucaGen treatment and observed 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. The estimated number of treatment episodes is 46.9 million over a 16 year period.

Therapeutic indication

| *System organ class* | *Subject incidence* | *Adverse drug reaction* |
|---|---|---|
| Immune system disorders | Very rare ≤ 1/10,000 | Hypersensitivity reactions including anaphylactic reaction |
| Gastrointestinal disorders | Common > 1/100 and ≤ 1/10<br>Uncommon >1/1,000 and ≤ 1/100<br>Rare > 1/10,000 and ≤ 1/1,000 | Nausea<br>Vomiting<br>Abdominal pain |
| General disorders and Administration site conditions | Unknown | Injection site reactions |

Diagnostic indication

| *System organ class* | *Subject incidence* | *Adverse drug reaction* |
|---|---|---|
| Immune system disorders | Very rare ≤ 1/10,000 | Hypersensitivity reactions including anaphylactic reaction |
| Metabolism and nutrition disorders | Uncommon > 1/1,000, and ≤ 1/100<br>Very rare ≤ 1/10,000 | Hypoglycaemia[1]<br>Hypoglycaemic coma |
| Cardiac disorders | Very rare ≤ 1/10,000<br>Very rare ≤ 1/10,000 | Bradycardia[2]<br>Tachycardia[2] |
| Vascular disorders | Very rare ≤ 1/10,000<br>Very rare ≤ 1/10,000 | Hypotension[2]<br>Hypertension[2] |
| Gastrointestinal disorders | Common > 1/100 and ≤ 1/10<br>Uncommon >1/1,000 and ≤ 1/100<br>Rare > 1/10,000 and ≤ 1/1,000 | Nausea<br>Vomiting<br>Abdominal pain |
| General disorders and Administration site conditions | Unknown | Injection site reactions |

[1] After a diagnostic procedure it can be more pronounced in patients having fasted (see 'section 4.4 Special Warnings and Precautions for Use').
[2] Cardiovascular adverse events have only been reported when GlucaGen HypoKit is used as an adjunct in endoscopic or radiographic procedures.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

## 4.9 Overdose

Glucagon is a safe drug and overdosage would not normally pose a significant danger. Nausea and vomiting would be expected and should be managed by general supportive measures. Due to the positive inotropic and chronotropic actions of glucagon, patients on β–blockers may experience a transient rise in blood pressure. At large doses (in excess of those recommended for normal clinical use) hypokalaemia may occur, and should be monitored and corrected, if needed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: H 04 AA 01.

Mechanism of action

Glucagon is a hyperglycaemic agent that mobilises hepatic glycogen which is released into the blood as glucose. Glucagon is only of benefit when liver glycogen is present. 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 cannot therefore assist in the transfer of carbohydrate from the much larger stores of glycogen that are present in skeletal muscles.

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 inhibits the tone and motility of the smooth muscles in the gastrointestinal tract.

Glucagon stimulates the production of insulin by the pancreatic beta cells and can, therefore, be used diagnostically in a C-peptide test to estimate residual β-cell capacity.

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

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

Clinical trials

No data available.

### 5.2 Pharmacokinetic Properties

Metabolism

The metabolism of exogenous glucagon is identical to that of endogenous glucagon which is as follows:

Glucagon is secreted by the alpha cells in the pancreatic Islets of Langerhans and transported via the portal circulation to the liver where the major portion is bound. From the liver it is excreted into the bile. The lesser portion of glucagon, that is not bound in the liver, is distributed to the other organs in the body, particularly the kidneys which have a high binding capacity for it. It is degraded enzymatically in blood plasma and in the organs to which it is distributed.

Excretion

The liver and kidney are major sites of glucagon clearance, each contributing about 30% to the overall metabolic clearance rate. Metabolic clearance of glucagon in humans is approximately 10 mL/kg/min. Glucagon has a short half-life in the blood of about 3 - 6 minutes.

### 5.3 Preclinical Safety Data

Genotoxicity
No data available.

Carcinogenicity
No data available.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients
Lactose monohydrate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

### 6.2 Incompatibilities
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 Shelf Life
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 Special Precautions for Storage
Store GlucaGen HypoKit below 25°C and in the original package in order to protect from light. Do not freeze, as this may cause damage to the glass syringe.

The solution must be prepared immediately prior to use. GlucaGen HypoKit does not contain a preservative. Use once only and discard any residue.

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

### 6.5 Nature and Contents of Container
GlucaGen HypoKit consists of a vial containing lyophilised glucagon (rys) 1 mg (1 IU) as hydrochloride and a glass syringe pre-filled with 1 mL water for injections. The powder vial is made of glass type I, Ph. Eur., is closed with a bromobutyl stopper, and is covered with an aluminium cap and a tamperproof plastic cap (the latter must be removed before use.) The pre-filled syringe (with needle) is made of glass type I, Ph. Eur. and contains a bromobutyl plunger.

### 6.6 Special Precautions for Disposal
In Australia, any unused medicine or waste material should be disposed of by takin it to your local pharmacy.

### 6.7 Physicochemical Properties

Chemical structure

CAS number
16941-32-5

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

S3

## 8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
Level 10
118 Mount Street
North Sydney NSW 2060
www.novonordisk.com.au

## 9. DATE OF FIRST APPROVAL

28 February 1994

## 10. DATE OF REVISION

21 September 2021

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 4.3 | Expansion of an existing precaution for monitoring of patients with cardiac disease; addition of a new precaution for short term hyperglycaemia associated with diagnostic use |
| 4.8 | Addition of Injection site reactions |
| 8 | Change to sponsors address |