Regulatory Operations

Insert: 2010-125x295-005
Current: 2

GlucaGen 1 languages with straight arrow

Colour: PMS 280C

GlucaGen® 1 mg

Powder and solvent for solution for injection

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 *List of excipients.*

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.

Clinical particulars

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.

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:
- Children below 25 kg or younger than 6-8 years: Administer 0.5 mg.
- Children above 25 kg or older than 6-8 years: Administer 1.0 mg.

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 *Instruction for use, handling and disposal.*

- ***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 carbohydrates 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 the end of the diagnostic procedure, oral carbohydrates should be given if this is compatible with the diagnostic procedure applied.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients.*
Phaeochromocytoma.

Special warnings and precautions for use
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.

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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.

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.

Caution should be observed when GlucaGen® is used as an adjunct in endoscopic or radiographic procedures in diabetic patients or in elderly patients with known cardiac disease.

Glucagon stimulates the release of catecholamines. In the presence of phaeochromocytoma, 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 *Contraindications*).

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.

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.

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.

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 has 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***

Immune system disorders
Very rare (< 1/10,000): Hypersensitivity reactions including anaphylactic reaction/shock.

Gastrointestinal disorders
Common (≥ 1/100 to < 1/10): Nausea
Uncommon (≥ 1/1,000 to < 1/100): Vomiting
Rare (≥ 1/10,000 to < 1/1,000): Abdominal pain.

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.

- ***Additional side effects after use in diagnostic procedures***

Metabolism and nutrition disorders
Uncommon (≥ 1/1,000 to < 1/100): Hypoglycaemia: After a diagnostic procedure this could be more pronounced in patients that have fasted (see *Special warnings and precautions for use*).
Very rare (< 1/10,000): Hypoglycaemic coma.

Cardiovascular disorders
Very rare (< 1/10,000): Tachycardia, hypotension, hypertension:
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.

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.

Pharmacological properties

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.

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.

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

Pharmaceutical particulars

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.

Incompatibilities
There are no known incompatibilities with GlucaGen®.

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® should be stored at a temperature of 2°C to 8°C (in a refrigerator). Store in the original package in order to protect from light.

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.

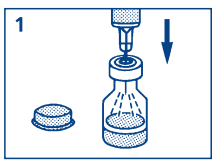
Container for solvent:
Vial made of glass type I, Ph. Eur., closed with a bromobutyl disc with teflon and covered with an aluminium cap.

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

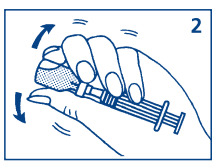
Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

Instruction for use, handling and disposal

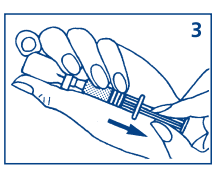
Reconstitution
The reconstituted GlucaGen® should be used immediately after preparation.



1. Remove 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 liquid from the syringe into the vial.

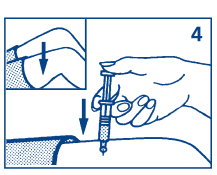


2. Without taking the needle out of the vial, gently shake the vial until GlucaGen® has completely dissolved, and the solution is clear.



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.

See *How much to use*.



4. Make an air shot and inject.

How much to use

The usual dosage for severe hypoglycaemia:
- Adults and children above 25 kg or older than 6-8 years: 1 ml
- Children below 25 kg or younger than 6-8 years: ½ ml.

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

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