GlucaGen® 1 mg

Powder and solvent for solution for injection

Qualitative and quantitative composition
Active substance: Glucagon, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).
Glucagon, rDNA is structurally identical to human glucagon.
- Glucagon 1 mg (1 IU) as hydrochloride.

One vial contains 1 mg glucagon corresponding to 1 mg glucagon/ml after reconstitution.
For excipients, see "Pharmaceutical Particulars".

Pharmaceutical form
Powder and solvent for solution for injection.

Clinical particulars

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

Diagnostic indication
Motility inhibition in examinations of the gastrointestinal tract.

Posology and method of administration

Therapeutic indication
(Severe hypoglycaemia)
Dosage for adult patients: Administer 1 mg.
Dosage for paediatric patients:
Administer 1 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 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.
Medical consultation is required for all patients with severe hypoglycaemia.

Diagnostic indication (Inhibition of 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 depending on the organ under examination. The onset of action after an intramuscular injection of 1-2 mg occurs after 5-15 minutes and lasts approximately 10-40 minutes depending on the organ.
After end of the diagnostic procedure, oral carbohydrates should be given to patients who have been fasting, if this is compatible with the diagnostic procedure applied.
The dose ranges from 0.2-2 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.

Contraindications
Hypersensitivity to glucagon or lactose.
Phaeocromocytoma.

Special warnings and precautions for use

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.

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, intravenously given glucose 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 also 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.

GlucaGen® should not be given via intravenous infusion.

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

Pregnancy and lactation
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.
Glucagon is cleared from the bloodstream very fast, mainly by the liver ($T_{1/2}$= 3-6 minutes); thus the amount excreted in the milk of nursing mothers following treatment of severe hypoglycaemic 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.

Effects on ability to drive and use machines
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 car should be avoided until the patient has had a meal with oral carbohydrates.

Undesirable effects
Frequencies of undesirable effects considered related to treatment with GlucaGen® during clinical trials and/or post-marketing surveillance 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. The estimated number of treatment episodes is 46.9 millions over a 16 year period.

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

Gastrointestinal disorders
Common (> 1/100, ≤ 1/10): Nausea
Uncommon (>1/1,000, ≤ 1/100): Vomiting
Rare (> 1/10,000, ≤ 1/1,000): Abdominal pain.

Additional side effects after use in diagnostic procedures

Metabolism and nutrition disorders
Uncommon (> 1/1,000, ≤ 1/100): Hypoglycaemia:
After a diagnostic procedure it can be more pronounced in patients having fasted, see "Special warnings and precautions for use".
Very rare (≤ 1/10,000): Hypoglycaemic coma.

Cardiavascular disorders
Very rare (≤ 1/10,000): Bradycardia, tachycardia, hypotension, hypertension: Cardiovascular undesirable effects have only been reported when GlucaGen® is used as an adjunct in endoscopic or radiographic procedures.

Overdose
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: H 04 AA 01.
Glucagon is a hyperglycaemic agent that mobilises 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 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 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 muscle in the gastrointestinal tract.

Phamacokinetic properties
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.
Glucagon has a short half-life in the blood of about 3-6 minutes.
Onset of effect occurs within 1 minute after an intravenous injection. Duration of action is in the range 5-20 minutes depending on dose and on the organ under examination. The onset of effect occurs within 5-15 minutes after an intramuscular injection, with the duration of 10-40 minutes depending on dose and organ.
When used in treatment of severe hypoglycaemia, an effect on blood glucose is usually seen within 10 minutes.

Preclinical safety data
The existing preclinical data reveal no hazard for humans.

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.

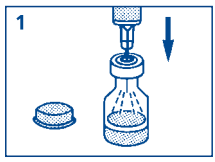
Incompatibilities
There are no known incompatibilities with GlucaGen®.

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.
Store in a refrigerator (2°C to 8°C) and in the original package in order to protect from light.
The reconstituted product should be used immediately after preparation.

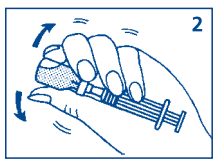
Nature and contents of container
Container for powder: Vial made of glass type I, Ph.Eur., closed with a bromobutyl stopper and covered with an aluminium cap.
Container for solvent: Vial made of glass type I, Ph.Eur., closed with a bromobutyl disc with teflon and covered with an aluminium cap.
The vials are provided with a tamperproof plastic cap which must be removed before use.

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

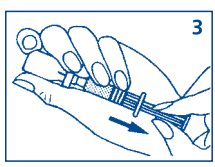
Instruction for use, handling and disposal
Reconstitution



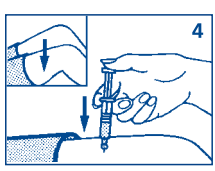
1. Remove the plastic caps from the vials. Draw up all the water into a disposable syringe.
Insert the needle through the rubber stopper (within the marked circle) of the vial containing GlucaGen® and inject all the liquid from the syringe into the vial.



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.



4. Make an air shot and inject.

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

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