SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Baqsimi 3 mg nasal powder in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose container delivers nasal powder with 3 mg of glucagon.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal powder in single-dose container (nasal powder).

White to practically white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus.

4.2 Posology and method of administration

Posology

Adults, adolescents and children aged 4 years and over
The recommended dose is 3 mg glucagon administered into one nostril.

Elderly (≥ 65 years)
No dose adjustment is required based on age.

Efficacy and safety data are very limited in patients aged 65 years and absent in patients aged 75 and above.

Renal and hepatic impairment
No dose adjustment is required based on renal and hepatic function.

Paediatric population 0 - < 4 years
The safety and efficacy of Baqsimi in infants and children aged 0 to < 4 years have not yet been established. No data are available.

<u>Method of administration</u>

Nasal use only. Glucagon nasal powder is given in a single nostril. Glucagon is passively absorbed through the nasal mucosa. It is not necessary to inhale or breathe deeply after dosing.

Instructions for administering glucagon nasal powder

1. Remove the shrink wrap by pulling on the red stripe.
2. Remove the single-dose container from the tube. Do not press the plunger until ready to give the dose.
3. Hold the single-dose container between fingers and thumb. Do not test before use as it contains only one dose of glucagon and cannot be reused.
4. Insert the tip of the single-dose container gently in one of the nostrils until finger(s) touch the outside of the nose.
5. Push the plunger all the way in. The dose is complete when the green line is no longer showing.
6. If the person is unconscious, turn the person on their side to prevent choking.
7. After giving the dose, the caregiver should call for medical help right away.
8. When the patient has responded to treatment, give oral carbohydrate to restore liver glycogen and prevent relapse of hypoglycaemia.

4.3 Contraindications

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

Phaeochromocytoma (see section 4.4).

4.4 Special warnings and precautions for use

<u>Phaeochromocytoma</u>

In the presence of phaeochromocytoma, glucagon may stimulate the release of catecholamines from the tumour. If the patient develops a dramatic increase in blood pressure, use of non-selective α-adrenergic blockade has been shown to

be effective in lowering blood pressure. Baqsimi is contraindicated in patients with phaeochromocytoma (see section 4.3).

Insulinoma

In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose. However, glucagon administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycaemia. A patient developing symptoms of hypoglycaemia after a dose of glucagon should be given glucose orally or intravenously.

Hypersensitivity and allergic reactions

Allergic reactions, which have been reported with injectable glucagon, may occur and include generalised rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. If the patient experiences difficulty breathing call for immediate medical assistance.

Glycogen stores and hypoglycaemia

Glucagon is effective in treating hypoglycaemia only if sufficient liver glycogen is present. Because glucagon is of little or no help in states of starvation, adrenal insufficiency, chronic alcohol abuse or chronic hypoglycaemia, these conditions should be treated with glucose.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Insulin
Reacts antagonistically towards glucagon

Indometacin

When used with indometacin, glucagon may lose its ability to raise blood glucose or may even produce hypoglycaemia.

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 transient because of glucagon's short half-life.

Glucagon treatment results in catecholamine release from the adrenal glands, and concomitant use of beta-blockers could result in unopposed alpha-

adrenergic stimulation and consequently, a greater increase in blood pressure (see section 4.4).

Warfarin

Glucagon may increase the anticoagulant effect of warfarin.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Reproduction and fertility studies with glucagon nasal powder were not conducted in animals.

Baqsimi can be used during 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.

Breast-feeding

Baqsimi can be used during breast-feeding Glucagon is cleared from the bloodstream very quickly and 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.

Fertility

No fertility studies have been conducted with glucagon nasal powder.

Studies in rats have shown that glucagon does not cause

4.7 Effects on ability to drive and use machines

Baqsimi has negligible influence on the ability to drive and use machines.

The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia which may persist for a brief period after receiving treatment. This may present a risk in situations where these abilities are especially important, such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are lacrimation increased (36 %), upper respiratory tract irritation (34 %), nausea (27 %), headache (21 %), and vomiting (16 %).

Tabulated list of adverse reactions

Adverse reactions are listed in table 1 as MedDRA preferred term by system organ class and frequency. The corresponding frequency category for each adverse reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 1. Frequency of adverse reactions of glucagon nasal powder

System Organ Class	Very common	Common	Uncommon
Nervous system disorders	Headache	Dysgeusia	
Eye disorders	Lacrimation increased	Ocular hyperaemia Eye pruritus	
Respiratory, thoracic, and mediastinal disorders	Upper respiratory tract irritation[a]		
Gastrointestinal disorders	Vomiting Nausea		
Skin and subcutaneous tissue disorders		Pruritus	
Investigations		Increased systolic blood pressure[b] Increased diastolic blood pressure[b]	Increased heart rate[b]

a **Upper respiratory tract irritation:** rhinorrhoea, nasal discomfort, nasal congestion, nasal pruritus, sneezing, throat irritation, cough, epistaxis, and parosmia

b **Increases in heart rate and blood pressure:** as assessed by vital sign measurements. Frequencies are based on shifts from pre-treatment to post-treatment values.

Immunogenicity
Overall, 5.6 % of patients developed treatment-emergent anti-glucagon antibodies. These antibodies were not neutralising and did not lower the efficacy of glucagon nor were they associated with the development of treatment-emergent adverse reactions.

Paediatric population

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

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 Yellow Card Scheme; Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

If overdose occurs, the patient may experience nausea, vomiting, inhibition of gastro-intestinal tract motility, increase in blood pressure and pulse rate. In case of suspected overdosing, serum potassium may decrease and should be monitored and corrected if needed. If the patient develops a dramatic increase in blood pressure, use of non-selective α-adrenergic blockade has been shown to be effective in lowering blood pressure for the short time that control would be needed (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pancreatic hormones, Glycogenolytic hormones, ATC code: H04AA01

Mechanism of action

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an anti-hypoglycaemic effect.

Pharmacodynamic effects

Gender and body weight had no clinically meaningful effect on the pharmacodynamics of glucagon nasal powder.

After administration of 3 mg glucagon nasal powder in adult patients with type 1 diabetes, glucose levels began to rise as early as 5 minutes (figure 1). By 10 minutes,

the median glucose level was above 3.9 mmol/L (70 mg/dL). The mean maximum glucose increase was 7.8 mmol/L (140 mg/dL).

In paediatric patients with type 1 diabetes (4 to < 17 years), after administration of 3 mg glucagon nasal powder, glucose levels began to rise as early as 5 minutes (figure 2) with a mean maximum glucose increase of 5.7 mmol/L (102 mg/dL) to 7.7 mmol/L (138 mg/dL).

Common cold with nasal congestion with or without concomitant use of a decongestant did not impact pharmacodynamics of glucagon nasal powder.

Figure 1. Mean glucose concentration over time in adult patients with type 1 diabetes.

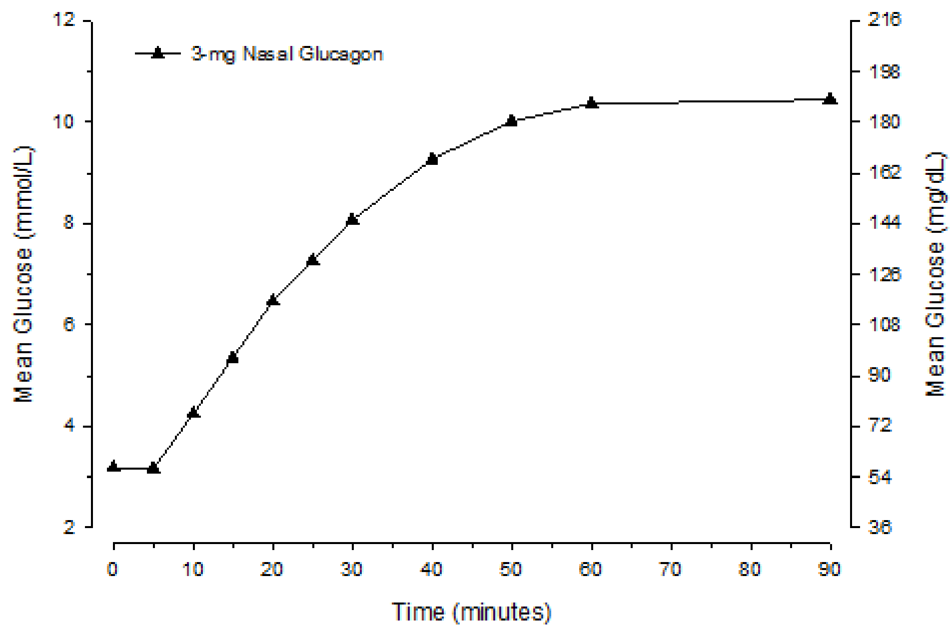
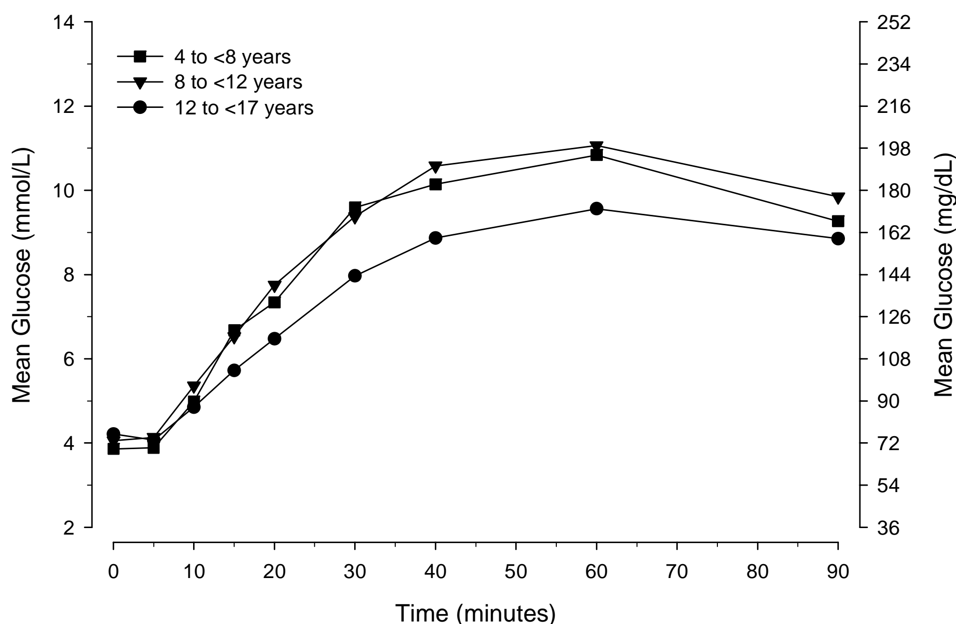


Figure 2. Mean glucose concentration over time in paediatric patients with type 1 diabetes.



Clinical efficacy

The adult pivotal study was a randomized, multicenter, open-label, 2-period, cross-over study in adult patients with type 1 diabetes or type 2 diabetes. The primary objective was to compare the efficacy of a single 3 mg dose of glucagon nasal powder against a 1 mg dose of intra-muscular (i.m.) glucagon in adult patients with type 1 diabetes. Insulin was used to reduce blood glucose levels to the hypoglycaemic range with a target blood glucose nadir of < 2.8 mmol/L (< 50 mg/dL).

The pivotal study enrolled 83 total patients 18 to < 65 years of age. Seventy-seven patients had type 1 diabetes, with a mean age of 32.9 years and a mean diabetes duration of 18.1 years, and 45 (58 %) patients were female. The mean age of patients with type 2 diabetes (n=6) was 47.8 years, with a mean diabetes duration of 18.8 years, and 4 (67 %) patients were female.

The primary efficacy outcome measure was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥ 3.9 mmol/L (≥ 70 mg/dL) or an increase of ≥ 1.1 mmol/L (≥ 20 mg/dL) from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level. Glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes, following glucagon administration.

For patients with type 1 diabetes, the mean nadir blood glucose was 2.5 mmol/L (44.2 mg/dL) for glucagon nasal powder and 2.7 mmol/L (48.9 mg/dL) for i.m. glucagon. Glucagon nasal powder demonstrated non-inferiority to i.m. glucagon in reversing insulin-induced hypoglycaemia with 98.7 % of glucagon nasal powder-treated patients and 100 % of i.m. glucagon-treated patients achieving treatment success within 30 minutes (table 2). All patients met glucose treatment success criteria within 40 minutes. All patients with type 2 diabetes (100 %) achieved treatment success within 30 minutes.

The mean time to treatment success was 16.2 and 12.2 minutes in the glucagon nasal powder and i.m. glucagon 1 mg treatment groups, respectively. Time to treatment success represents the time from glucagon administration to patient achieving treatment success; it does not include the time for reconstitution and preparation of the intra-muscular injection in the control group.

By 30 minutes post glucagon administration, patients in both glucagon nasal powder and i.m. glucagon groups had similar improvement in symptoms of hypoglycaemia, as evaluated by Edinburgh Hypoglycaemia Symptom Questionnaire.

Table 2. Patients meeting treatment success and other glucose criteria in pivotal study

	Type 1 diabetes (n=75)[a]		**Type 1 and type 2 diabetes (n=80)[a]**	
	glucagon nasal powder 3 mg	**i.m. glucagon 1 mg**	**glucagon nasal powder 3 mg**	**i.m. glucagon 1 mg**
Treatment success – n (%)	74 (98.7 %)	75 (100 %)	79 (98.8 %)	80 (100 %)
Treatment difference (2-sided 95 % confidence interval)[b,c]	1.3% (-3.8%, 7.2%)		1.3% (-3.6%, 6.8%)	
Glucose criterion met – n (%)[d]				
(i) ≥ 3.9 mmol/L (≥ 70 mg/dL)	72 (97 %)	74 (99 %)	77 (97 %)	79 (99 %)
(ii) Increase by ≥ 1.1 mmol/L (≥ 20 mg/dL) from nadir	74 (100 %)	75 (100 %)	79 (100 %)	80 (100 %)
Both (i) and (ii)	72 (97 %)	74 (99 %)	77 (97 %)	79 (99 %)

[a] The efficacy analysis population consisted of all patients who received both doses of the study medicinal product with evaluable primary outcome.
[b] Difference calculated as (percentage with success in i.m. glucagon) – (percentage with success in glucagon nasal powder).
[c] 2-sided 95 % confidence interval (CI) using the unconditional profile likelihood method based on ‘exact’ tail areas; non-inferiority margin=10 %.
[d] Percentage based on number of patients meeting treatment success.

In a similarly designed clinical confirmatory study, 70 patients with type 1 diabetes were enrolled with a mean age of 41.7 years (20-64 years), and a mean diabetes duration of 19.8 years. Twenty-seven (39%) were female. Insulin was used to reduce blood glucose levels to < 3.3 mmol/L (< 60 mg/dL).

The mean nadir blood glucose was 3.0 mmol/L (54.2 mg/dL) for glucagon nasal powder and 3.1 mmol/L (55.7 mg/dL) for i.m. glucagon. Glucagon nasal powder demonstrated non-inferiority to i.m. glucagon in reversing insulin-induced hypoglycaemia with 100 % of glucagon nasal powder-treated patients and 100 % of i.m. glucagon-treated patients achieving treatment success (table 3). The mean time to treatment success was 11.4 and 9.9 minutes in the glucagon nasal powder and i.m. glucagon 1 mg treatment groups, respectively.

Table 3. Patients meeting treatment success and other glucose criteria in confirmatory study

	Type 1 diabetes (n=66)[a]	
	glucagon nasal powder 3 mg	**i.m. glucagon 1 mg**
Treatment success – n (%)	66 (100 %)	66 (100 %)
Treatment difference (2-sided 95 % confidence interval)[b,c]	0 % (-5.4%, 5.4%)	
Glucose criterion met – n (%)		
(i) ≥ 3.9 mmol/L (≥70 mg/dL)	66 (100 %)	66 (100 %)
(ii) Increase by ≥ 1.1 mmol/L (≥ 20 mg/dL) from nadir	66 (100 %)	66 (100 %)
Both (i) and (ii)	66 (100 %)	66 (100 %)

[a] The efficacy analysis population consisted of all patients who received both doses of the study medicinal product with evaluable primary outcome.
[b] Difference calculated as (percentage with success in i.m. glucagon) – (percentage with success in glucagon nasal powder); non-inferiority margin = 10 %.
[c] 2-sided 95 % confidence interval (CI) using the unconditional profile likelihood method based on 'exact' tail areas.

In an adult actual use study of approximately 6 months duration, 129 patients with type 1 diabetes (mean age, 46.6 years; range, 18 to 71 years) and their caregivers were dispensed glucagon nasal powder to treat moderate or severe hypoglycaemic events in the home or work setting. A total of 157 moderate or severe hypoglycaemic events reported by 69 patients were included in the efficacy analysis. An episode of severe hypoglycaemia was defined as an episode wherein the person with diabetes is clinically incapacitated (that is, unconscious, convulsions, severe mental disorientation) to the point where the person requires third-party assistance to treat the hypoglycaemia. An episode of moderate hypoglycaemia was defined as an episode wherein the person with diabetes was showing signs of neuroglycopenia (that is, weakness, difficulty speaking, double vision, drowsiness, inability to concentrate, blurred vision, anxiety, hunger, tiredness or confusion) and had a glucometer reading of approximately 60 mg/dL (3.3 mmol/L) or less. In 151 (96.2 %) of these events, patients awoke or returned to normal status within 30 minutes following glucagon nasal powder administration. In all (100 %) 12 severe hypoglycaemic events, patients awoke, stopped convulsions (7 events from 4 patients having presented with convulsions before glucagon nasal powder dosing) or returned to normal status within 5 to 15 minutes following glucagon nasal powder administration.

Paediatric population

The paediatric pivotal study was a randomized, multicenter, clinical study that assessed glucagon nasal powder compared to i.m. glucagon in children and adolescents with type 1 diabetes. Glucagon was administered after glucose reached < 4.4 mmol/L (< 80 mg/dL) on the dosing day. Efficacy was assessed based on percentage of patients with a glucose increase of ≥ 1.1 mmol/L (≥ 20 mg/dL) from glucose nadir within 30 minutes following glucagon administration.

Forty-eight patients were enrolled and received at least one dose of study medicinal product. The mean age in the young children cohort (4 to < 8 years) was 6.5 years. In

the children cohort (8 to < 12 years), mean age was 11.1 years and in the adolescents cohort (12 to < 17 years) mean age was 14.6 years. In all age cohorts, the population was predominantly male and white.

Across all age groups, 3 mg glucagon nasal powder and i.m. glucagon 0.5 mg (children below 25 kg) or 1 mg (children 25 kg or above), demonstrated similar glycemic responses. All (100 %) patients in both treatment arms across all age groups achieved an increase in glucose ≥ 1.1 mmol/L (≥ 20 mg/dL) from glucose nadir within 20 minutes of glucagon administration.

The mean time to reach a glucose increase of ≥ 1.1 mmol/L (≥ 20 mg/dL) was similar between glucagon nasal powder and i.m. glucagon for all age groups (table 4).

Table 4. Mean time to reach glucose increase of ≥ 1.1 mmol/L (≥ 20 mg/dL) from nadir in paediatric pivotal study

Increase from nadir	**Mean time post-glucagon administration (minutes)**					
	Young children (4 to < 8 years old)		**Children (8 to < 12 years old)**		**Adolescents (12 to < 17 years old)**	
	i.m. glucagon[a] n=6	**glucagon nasal powder 3 mg n=12**	**i.m. glucagon[a] n=6**	**glucagon nasal powder 3 mg n=12**	**i.m. glucagon[a] n=12**	**glucagon nasal powder 3 mg n=12**
≥ 1.1 mmol/L (≥ 20 mg/dL)	10.0	10.8	12.5	11.3	12.5	14.2

[a] 0.5 mg or 1 mg of i.m. glucagon (based upon body weight)

In a paediatric actual use study of approximately 6 months duration, 26 patients aged 4 to < 18 years old with type 1 diabetes (mean age, 11.7 years; range, 5 to 17 years) and their caregivers were dispensed 3 mg glucagon nasal powder to treat moderate including major hypoglycaemic events in the home or school setting. A total of 33 moderate hypoglycaemic events reported by 14 patients were included in the efficacy analysis. An episode of major hypoglycaemia was defined as an episode with neuroglycopenia symptoms and a glucose level below 50 mg/dL (2.8 mmol/L). An episode of moderate hypoglycaemia is defined as an episode wherein the child/adolescent with diabetes has symptoms and/or signs of neuroglycopenia and has a blood glucose level of ≤ 70 mg/dL (3.9 mmol/L). In all events, including major hypoglycaemia (8 events from 5 patients), patients returned to normal status within 5 to 30 minutes following glucagon nasal powder administration.

The European Medicines Agency has deferred the obligation to submit the results of studies with Baqsimi in one or more subsets of the paediatric population in the treatment of severe hypoglycaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Glucagon absorption via the nasal route achieved mean peak plasma levels of 6130 pg/mL at 15 minutes.

Distribution

The apparent volume of distribution of glucagon was approximately 885 L via the nasal route.

Biotransformation

Glucagon is known to be degraded in the liver, kidneys, and plasma.

Elimination

The mean half-life of glucagon was approximately 38 minutes via the nasal route.

Renal and hepatic impairment

No formal studies have been performed to evaluate renal or hepatic impairment.

Paediatric population

In paediatric patients (4 to < 17 years), glucagon absorption via the nasal route, achieved mean peak plasma levels between 15 and 20 minutes.

Common cold and use of degongestant

Common cold with nasal congestion with or without concomitant use of a decongestant did not impact pharmacokinetics via the nasal route.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and local tolerance with glucagon nasal powder.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex (E459)
Dodecylphosphocholine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30 °C.

Keep the single-dose container in the shrink wrapped tube until ready to use in order to protect from moisture.

If the tube has been opened, the single-dose container may have been exposed to moisture. This could cause the medicinal product to not work as expected. Examine the shrink wrapped tube periodically. If the tube has been opened, replace the medicinal product.

6.5 Nature and contents of container

The single-dose container consists of polyethylene and polypropylene. The shrink wrapped tube is comprised of polyethylene and polypropylene containing a desiccant.

Pack sizes of 1 or 2 single-dose containers. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for use

This is a ready to use medicinal product and for single-use only.

The single-dose container contains only one dose and therefore it must not be primed or tested prior to use.

The instructions for using the medicinal product in the package leaflet must be followed carefully.

Discard nasal glucagon single-dose container and tube after use.

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

7 MARKETING AUTHORISATION HOLDER

International Medication Systems (UK) Ltd
First Floor, Templeback
10 Temple Back
Bristol
United Kingdom
BS1 6FL

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 03265/0079

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

18/01/2024