ANNEX I

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
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 impairment
No dose adjustment is required based on renal function.

Hepatic impairment
No dose adjustment is required based on hepatic function.

Paediatric population aged 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.

Method of administration

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.

Patients and their caregivers should be instructed on the signs and symptoms of severe hypoglycaemia. As severe hypoglycaemia requires the help of others to recover, the patient should be instructed to inform those around them about Baqsimi and its package leaflet. Baqsimi should be administered as

soon as possible when severe hypoglycaemia is recognised. The patient or caregiver should be instructed to read the package leaflet. The following instructions should be emphasised:

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.

For special warnings and precautions for use see section 4.4.

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

Phaeochromocytoma

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

Insulin reacts antagonistically towards glucagon.

Indomethacin

When used with indomethacin, 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 impaired fertility.

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 aged 4 years and above 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 the national reporting system listed in Appendix V.

4.9 Overdose

If overdose occurs, the patient may experience nausea, vomiting, inhibition of gastrointestinal 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 (see 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 (aged 4 to < 17 years), after administration of 3 mg glucagon nasal powder, glucose levels began to rise as early as 5 minutes (see 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

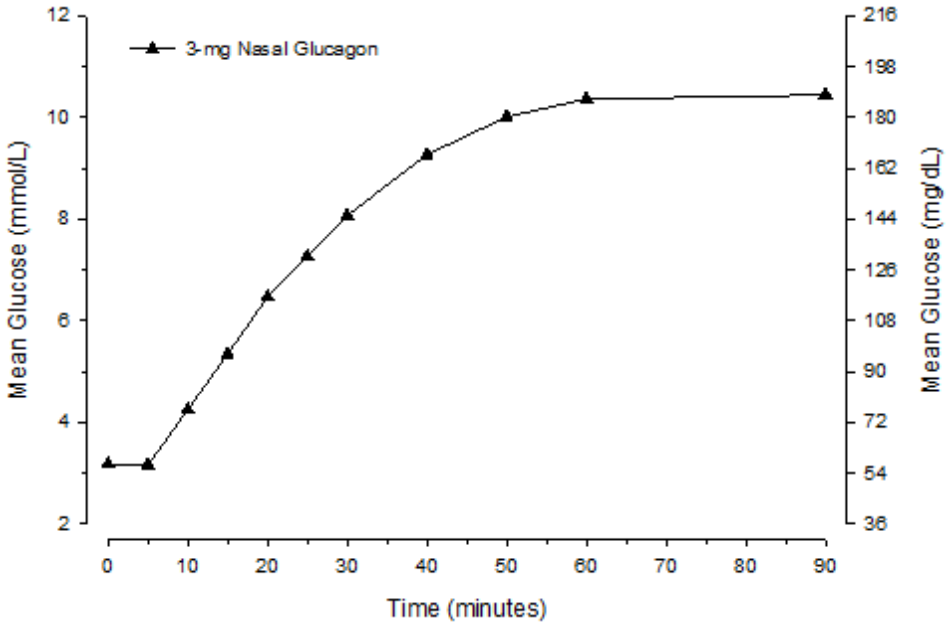
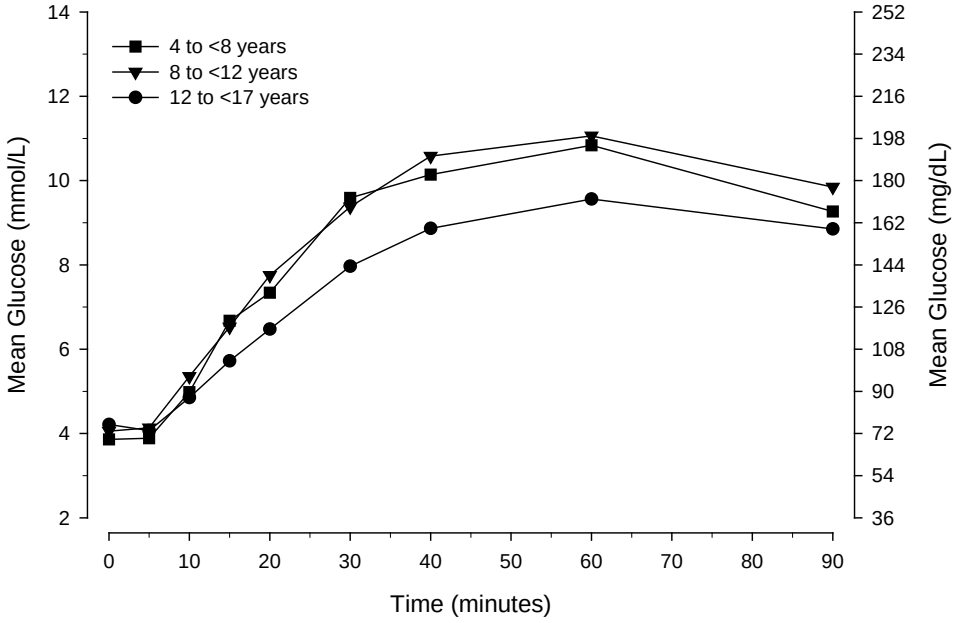


Figure 2. Mean glucose concentration over time in paediatric patients with type 1 diabetes



Clinical efficacy

The adult pivotal study was a randomized, multicentre, 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 intramuscular 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 aged 18 to < 65 years. 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 intramuscular glucagon. Glucagon nasal powder demonstrated non-inferiority to intramuscular glucagon in reversing insulin-induced hypoglycaemia with 98.7% of glucagon nasal powder-treated patients and 100 % of intramuscular glucagon-treated patients achieving treatment success within 30 minutes (see 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 intramuscular 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 intramuscular 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	**intramuscular glucagon 1 mg**	**glucagon nasal powder 3 mg**	**intramuscular 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 intramuscular 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 mmol/L (54.2 mg/dL) for glucagon nasal powder and 3.1 mmol/L (55.7 mg/dL) for intramuscular glucagon. Glucagon nasal powder demonstrated non-inferiority to intramuscular glucagon in reversing insulin-induced hypoglycaemia with 100% of glucagon nasal powder-treated patients and 100% of intramuscular glucagon-treated patients achieving treatment success (see table 3). The mean time to treatment success was 11.4 and 9.9 minutes in the glucagon nasal powder and intramuscular 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	**intramuscular 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 intramuscular 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 randomised, multicentre, clinical study that assessed glucagon nasal powder compared to intramuscular 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 intramuscular glucagon 0.5 mg (children below 25 kg) or 1 mg (children 25 kg or above), demonstrated similar glycaemic 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 intramuscular glucagon for all age groups (see 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)	
	intra-muscular glucagon[a] n=6	glucagon nasal powder 3 mg n=12	intra-muscular glucagon[a] n=6	glucagon nasal powder 3 mg n=12	intra-muscular 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 intramuscular 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 6 130 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 impairment

No formal studies have been performed to evaluate renal impairment.

Hepatic impairment

No formal studies have been performed to evaluate hepatic impairment.

Paediatric population

In paediatric patients (aged 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 decongestant

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, genotoxicity, carcinogenic potential, toxicity to reproduction and development..

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.

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 and other handling

Handling

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.

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.

Disposal

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

Amphastar France Pharmaceuticals
Usine Saint Charles
Eragny Sur Epte
60590
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1406/001
EU/1/19/1406/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2019
Date of latest renewal: 22 August 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Amphastar France Pharmaceuticals
Usine Saint Charles
Eragny Sur Epte
60590
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Baqsimi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at providing guidance on how to minimise the important potential risk in the RMP of inappropriate use of the device leading to loss of drug benefit.

The MAH shall ensure that in each Member State where Baqsimi is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use Baqsimi have access to/are provided with the following educational package:

- Administration leaflet;
- Instructional video;

- Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device.

The **administration leaflet** should contain the following key elements:

- Patients should receive the administration leaflet from their healthcare professionals upon initial Baqsimi prescription and after training.
- The demonstration kit should include a leaflet unique to the trainer device.
- It is important not to prime the single-dose container in advance, not to remove the shrink wrapping or to remove the single-dose container from the tube in advance and to ensure that the patient understands that while the trainer device used during demonstration can be reset/reused, each Baqsimi single-dose container can only be used once.
- The PL/IFU should be referenced for more detailed information regarding administration and handling of Baqsimi.
- Patients can use the leaflet to teach those around them how to correctly handle and administer Baqsimi.
- The leaflet should contain a URL and, where required, a password to a website where patients can access the instructional video.

The **instructional video** should contain the following key elements:

- To reinforce the correct Baqsimi handling and administration, step-by-step instructions on the appropriate use of Baqsimi should be provided.

The **demonstration kit that includes a trainer device** should contain the following key elements:

- The demonstration kit consists of a trainer device, which is a non-drug containing device, and a box with instructions on how to use Baqsimi.
- An administration leaflet unique to the trainer device should be included within the demonstration kit that includes the trainer device.
- The trainer device should be used by healthcare professionals who prescribe and supply Baqsimi to educate patients and/or caregivers.
- In addition to instructions for correct handling and administration, the demonstration kit should contain key points that healthcare professionals who prescribe and supply Baqsimi should emphasise when training patients and/or caregivers on Baqsimi (importance of not priming the single-dose container in advance, not removing the shrink wrapping or removing the single-dose container from the tube in advance and ensuring that the patient understands that while the trainer device used during demonstration can be reset/reused, each Baqsimi single-dose container can only be used once).
- The trainer device should not be inserted into a patient’s nostril when demonstrating (that is, to observe prudent hygiene measures).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Baqsimi 3 mg nasal powder in single-dose container
glucagon

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: betadex (E459) and dodecylphosphocholine.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal powder in single-dose container

1 single-dose container
2 single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Nasal use.
For single use only.
Do not press the plunger prior to insertion as you will lose the dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amphastar France Pharmaceuticals
Usine Saint Charles
Eragny Sur Epte
60590
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1406/001 1 single-dose container
EU/1/19/1406/002 2 single-dose containers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Baqsimi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABEL – Tube

1. NAME OF THE MEDICINAL PRODUCT

Baqsimi 3 mg nasal powder in single-dose container
glucagon

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amphastar France Pharmaceuticals

3. EXPIRY DATE

EXP

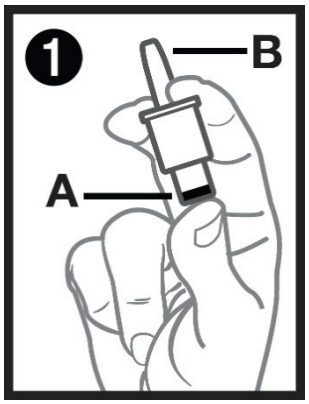
4. BATCH NUMBER

Lot

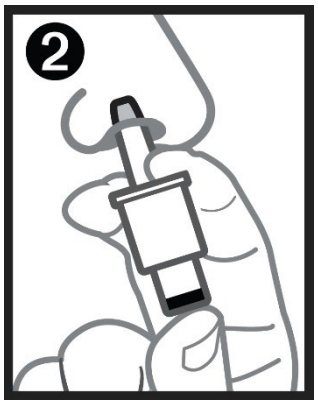
5. OTHER

Nasal use
Single use only

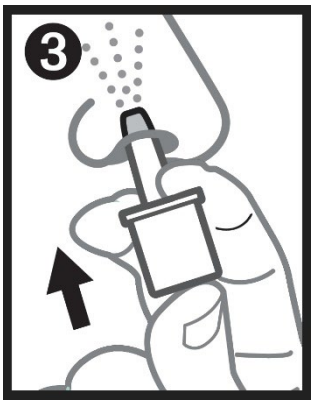
Instructions:



1. HOLD the single-dose container as shown. **Do not press plunger (A) before insertion.**



2. INSERT Tip (B) in one of the nostrils**.**



3. PUSH the Plunger (A) all the way in until **the green line is no longer showing.**

Do not remove shrink wrap until ready to use.
Peel for instructions after giving the dose.

<u>After giving the dose:</u>

- If the person is unconscious, turn the person on their side after giving Baqsimi.
- **Call for medical help right away.**
- Encourage the person to eat or drink a high sugar snack like sweets or fruit juice as soon as possible.
- **Throw away the used single-dose container and tube.**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL – Single-dose container

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Baqsimi 3 mg nasal powder
glucagon
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Baqsimi 3 mg nasal powder in single-dose container
glucagon

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Baqsimi is and what it is used for

Baqsimi contains the active substance glucagon, which belongs to a group of medicines called glycogenolytic hormones. It is used to treat severe hypoglycaemia (very low blood sugar) in people with diabetes. It is for use in adults, adolescents, and children aged 4 years or older.

Glucagon is a natural hormone produced by the pancreas. It works in the opposite way to insulin and raises blood sugar. It does this by converting stored sugar in the liver called glycogen to glucose (a form of sugar that the body uses for energy). The glucose then enters the bloodstream and raises the blood sugar level, so reducing the effects of hypoglycaemia.

You should always carry Baqsimi with you and tell your friends and family that you are carrying it.

2. What you need to know before you are given Baqsimi

Important information
If you are at risk of severe hypoglycaemia you should always have Baqsimi readily available:
- show your family members, friends, or people you work with where you keep this medicine and explain when and how to use it. Delay in treatment may be harmful. It is important they know how to use Baqsimi before you need it.

Do not use Baqsimi
- if you are allergic to glucagon or any of the other ingredients of this medicine (listed in section 6).
- if you have phaeochromocytoma, which is a tumour in the adrenal gland (a gland above your kidneys).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Baqsimi:
- if you have a tumour in your pancreas called insulinoma.
- if you have insufficient liver glycogen. This could occur:

- in states of starvation.
- if your adrenal gland does not produce enough cortisol or aldosterone.
- if you suffer from chronic hypoglycaemia.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Baqsimi.

If you have an allergic reaction to glucagon with generalised rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension, call for immediate medical assistance.

After using Baqsimi, eat as soon as possible to prevent the recurrence of low blood sugar. Take a fast-acting source of sugar, such as fruit juice or a sugar-containing carbonated drink.

Children
Baqsimi is not recommended for children under 4 years of age because it has not been studied in this age group.

Other medicines and Baqsimi
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

The following medicines can affect the way Baqsimi works:
- insulin, used to treat diabetes. Insulin has the opposite effect of glucagon on blood sugar.
- indomethacin, used to treat joint pain and stiffness. Indomethacin reduces the effect of glucagon or may even produce hypoglycaemia.

The following medicines may be affected by Baqsimi:
- warfarin, used to prevent blood clots. Baqsimi may increase the anticlotting effect of warfarin.
- beta-blockers, used to treat high blood pressure and irregular heart beat. Baqsimi may increase blood pressure and pulse. This will only last a short time.

Pregnancy and breast-feeding
If your blood sugar drops very low when you are pregnant or breast-feeding, you can use Baqsimi.

Driving and using machines
Wait until the effects of very low blood sugar have worn off, before driving or using any tools or machines.

3. How Baqsimi is given

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Explain how to use Baqsimi to your family, friends, co-workers or caregiver. They will need to know how to use it before you need it.

Baqsimi is given as a single 3 mg dose.

Instructions for giving Baqsimi
1. Remove the shrink wrap by pulling on the red stripe.
2. Open the lid and remove the single-dose container from the tube.

Caution: Do not press the plunger before insertion into the nose, otherwise the single dose in the single-dose container will be lost.

Giving the dose

1. 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.
2. Insert the tip gently into a nostril until the finger touches the outside of the nose.
3. Push the plunger all the way in with your thumb. The dose is complete when the green line no longer shows on the plunger.
4. If the person with the low blood sugar is unconscious, turn the person to their side to prevent choking.
5. After giving the dose, call for medical help right away.
6. Encourage the person with the low blood sugar to eat as soon as possible. A high sugar snack will stop another fall in blood sugar level.

Read the "Instructions for Use" carefully before using Baqsimi.

If you are given more Baqsimi than you should
Too much Baqsimi may cause nausea and vomiting. It may also raise your blood pressure and pulse rate. Specific treatment is not usually necessary.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects that may affect more than 1 in 10 people using this medicine are:
- Headache
- Watery eyes
- Discomfort and other effects in the nose, including itchiness, sneezing, runny or blocked nose and bleeding
- Throat irritation and cough
- Altered sense of smell
- Vomiting (being sick)
- Nausea (feeling sick)

Common side effects that may affect up to 1 in 10 people using this medicine are:
- Altered sense of taste
- Red eyes
- Itchy eyes
- Itchy skin
- Increased blood pressure

Uncommon side effects that may affect up to 1 in 100 people using this medicine are:
- Increased heart rate

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Baqsimi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, tube and single-dose container after EXP. The expiry date refers to the last day of that month.

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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Baqsimi contains
- The active substance is glucagon. Each single-dose container delivers nasal powder with 3 mg of glucagon.
- The other ingredients are betadex (E459) and dodecylphosphocholine.

What Baqsimi looks like and contents of the pack
Baqsimi is a white to practically white nasal powder in single-dose container (nasal powder).
Each single-dose container contains a single dose of glucagon nasal powder.
Baqsimi is packed in a carton containing 1 or 2 single-dose containers individually sealed in a plastic tube. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Amphastar France Pharmaceuticals
Usine Saint Charles
Eragny Sur Epte
60590
France

Manufacturers
Amphastar France Pharmaceuticals
Usine Saint Charles
Eragny Sur Epte
60590
France

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

INSTRUCTIONS FOR USE

Baqsimi 3 mg nasal powder in single-dose container
glucagon

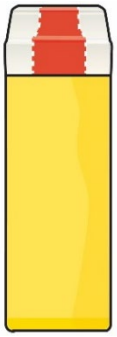
Read the instructions for use before using Baqsimi. Also read the package leaflet in full before using the medicine.

- Show your family and friends where you keep Baqsimi and explain how to use it by sharing these instructions. **They need to know how to use it before you need it.**
- Baqsimi is used to treat severe low blood sugar (hypoglycaemia).

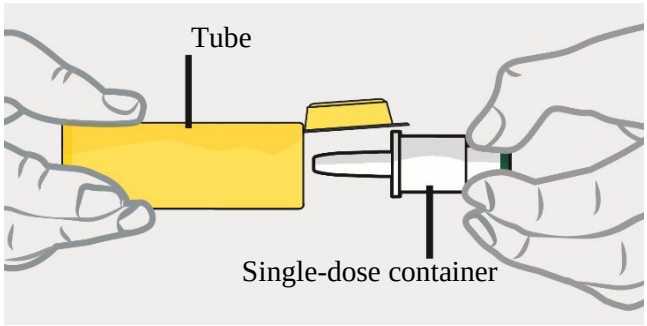
IMPORTANT POINTS TO KNOW

- **Keep** the single-dose container in the shrink-wrapped tube until it needs to be used in order to protect from moisture**.**
- If the tube has been opened, moisture may have got into the single-dose container and medicine may not work properly.
- Baqsimi contains only 1 dose of glucagon so **do not press plunger before inserting into nose**.
- Baqsimi is for use in the nose and for single use only.

PREPARING THE DOSE



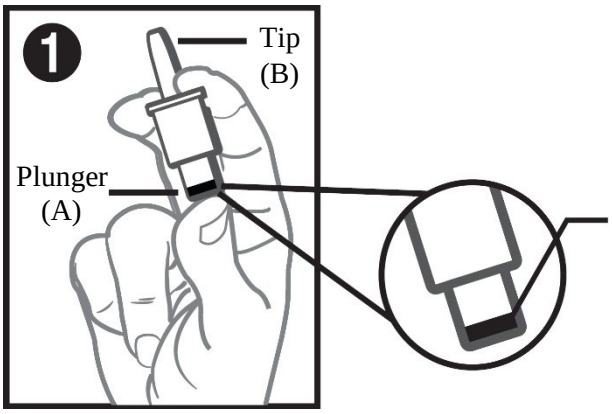
- Remove the shrink wrap by pulling on red stripe.



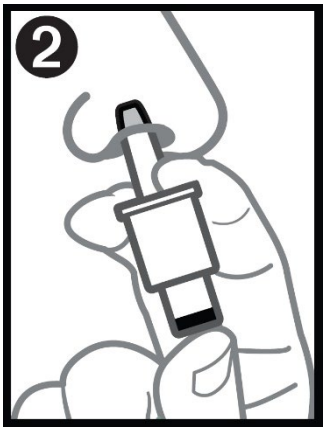
- Open the lid and remove the single-dose container from the tube.

Caution: Do not press the plunger before insertion into the nose.
Otherwise the single dose in the single-dose container will be lost.

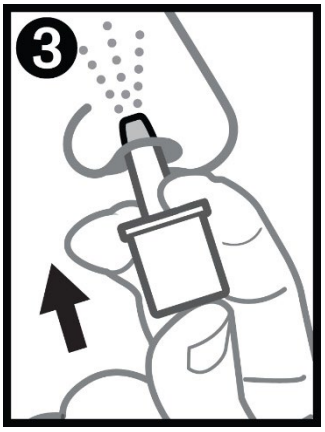
GIVING THE DOSE



- Hold the single-dose container between fingers. **Do not press plunger (A) or test single-dose container.**



- Insert the tip (B) gently in a nostril **until the finger touches the outside of the nose.**



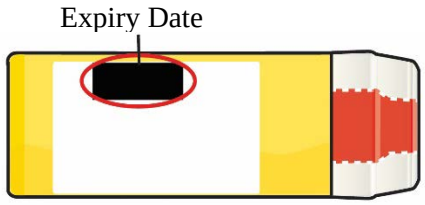
- Push the plunger (A) all the way in with your thumb.
- The dose is complete **when the green line on the plunger no longer shows**.

AFTER GIVING THE DOSE

- If the person with the low blood sugar is unconscious, turn the person to their side after giving Baqsimi.
- Remove the tip from nose.
- **Call for medical help right away.**
- Encourage the person with the low blood sugar to eat or drink a high sugar snack like sweets or fruit juice as soon as possible.
- Throw away the used single-dose container and tube.

STORAGE AND HANDLING

- **Do not remove the shrink-wrapping or open the tube until ready to give the dose.**
- Store the single-dose container in the shrink-wrapped tube at temperatures up to 30 ºC.
- Replace Baqsimi before the expiry date printed on the tube or carton.



OTHER INFORMATION

- **Caution: Replace the used Baqsimi right away so you will have a new Baqsimi in case you need it.**
- Keep Baqsimi out of the sight and reach of children.

FOR QUESTIONS OR MORE INFORMATION ABOUT BAQSIMI

- Ask your doctor, pharmacist or nurse.