PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BAQSIMI®

glucagon nasal powder

Powder; 3 mg glucagon per device; nasal

Hyperglycemic Agent

Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, CA
91730, USA

Imported and distributed by:
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Date of Preparation:
February 14, 2024

Submission Control No: 282911

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BAQSIMI is indicated for the treatment of severe hypoglycemic reactions which may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates.

1.1 Pediatrics

Pediatrics (<18 years of age): BAQSIMI is indicated in children 4 years and above. BAQSIMI has not been studied in pediatric patients less than 4 years of age. The number of pediatric patients (4 to <18 years) included in the clinical trials is limited (n=48) (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, and CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (≥65 years of age): Clinical studies of BAQSIMI did not include sufficient numbers of subjects aged 65 and over. Limited clinical trial experience with BAQSIMI has not identified differences in responses between the elderly and younger patients (see WARNINGS AND PRECAUTIONS, Special Populations; DOSAGE AND ADMINISTRATION; and ACTION AND CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

BAQSIMI is contraindicated in patients with:

- Known hypersensitivity to glucagon or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Pheochromocytoma
- Insulinoma

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

BAQSIMI should be given only in patients where impaired consciousness precludes oral carbohydrates. After intranasal administration the patient will normally respond within 15 minutes. If the patient does not respond within 15 minutes, intravenous (IV) glucose must be administered as soon as IV access can be established.

Because glucagon is of little or no help in states of starvation, adrenal insufficiency, or chronic hypoglycemia, intravenous glucose should be used for the treatment of hypoglycemia in these conditions.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

The recommended dose of BAQSIMI is 3 mg given intranasally in both adult and pediatric patients.

4.2 Administration

Instruct the patient or caregiver to read the package leaflet at the time they receive BAQSIMI.

Because BAQSIMI is designed to be administered in emergency situations to the patient by caregiver(s), where a high level of stress is likely, it is therefore important that the patient is instructed to make sure that family, friends and co-workers know where, when and how to use BAQSIMI.

Specific instructions on the use of BAQSIMI should be given to patients at risk of hypoglycemia unawareness, including elderly.

Emphasize the following instructions to the patient and/or caregiver:

- BAQSIMI is for intranasal use only. The recommended dose of BAQSIMI is 3 mg administered as one actuation of the intranasal device into one nostril.
- Read and follow the instructions on the package leaflet enclosed with BAQSIMI.
- Do not push the plunger or test the device prior to administration.
- Administer the dose by inserting the tip into one nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
- Call for medical help right away after giving the dose.
- Give oral carbohydrates when the patient responds to treatment.
- If the patient does not respond within 15 minutes, intravenous glucose must be administered as soon as IV access can be established. Medical consultation is required for all patients with severe hypoglycemia so that the dose of insulin and oral antidiabetic medication may be adjusted more accurately.
- Each BAQSIMI device contains one dose of glucagon and cannot be reused.

5 OVERDOSAGE

If overdose occurs, the patient may experience nausea, vomiting, diarrhea, inhibition of GI tract motility or an increase in blood pressure and pulse rate.

In case of suspected overdosing, the serum potassium may decrease and should be monitored and corrected if needed.

If the patient develops a dramatic increase in blood pressure, phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intranasal	Powder / 3 mg glucagon per device	Betadex and dodecylphosphocholine (DPC)

BAQSIMI is a single use nasal dosing device containing 3 mg of glucagon administered as one actuation of the intranasal device into one nostril.

A BAQSIMI single-pack contains 1 shrink wrapped tube that contains 3 mg of glucagon in a single use nasal dosing device.

A BAQSIMI two-pack contains 2 shrink wrapped tubes that each contain 3 mg of glucagon in a single use nasal dosing device.

Not all pack sizes may be marketed.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX, Part I: Health Professional Information.

General

BAQSIMI 3 mg by intranasal administration, is helpful in treating hypoglycemia only if sufficient liver glycogen is present.

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

Carcinogenesis and Mutagenesis

(see NON-CLINICAL TOXICOLOGY)

Cardiovascular

In high concentrations, glucagon exerts positive inotropic and chronotropic effect and may therefore cause tachycardia and acute hypertensive reactions (see CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Driving and Operating Machinery

No studies on the effects of glucagon on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating machinery.

Endocrine and Metabolism

Pheochromocytoma

BAQSIMI is contraindicated in patients with pheochromocytoma (see CONTRAINDICATIONS). In the presence of pheochromocytoma, glucagon may stimulate the release of catecholamines from the tumor which results in a sudden and marked increase in blood pressure. If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Insulinoma

BAQSIMI is contraindicated in patients with insulinoma (see CONTRAINDICATIONS). Glucagon administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia.

Sensitivity/Resistance
BAQSIMI is contraindicated in patients with a prior hypersensitivity reaction (see CONTRAINDICATIONS). Generalized allergic reactions including urticaria, respiratory distress, and hypotension (anaphylactic reaction/shock), have been reported in patients who received glucagon.

7.1 Special Populations

7.1.1 Pregnant Women

No clinical studies with BAQSIMI have been performed in pregnant women. Glucagon does not cross the human placental barrier.

7.1.2 Breast-feeding

No clinical studies have been performed in nursing mothers. Safe use of BAQSIMI during lactation has not been established, and it is not known whether glucagon is excreted in human milk. Intact glucagon is not absorbed from the GI tract. Therefore, even if the infant ingested glucagon it would be unlikely to have any metabolic effect on the infant.

7.1.3 Pediatrics

Pediatrics (4 to <18 years of age): BAQSIMI has not been studied in pediatric patients below the age of 4. The number of pediatric patients (4 to <18 years) included in the clinical trials is limited (n=48). Based on the data submitted to and reviewed by Health Canada, BAQSIMI is safe and effective in pediatric patients (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, and CLINICAL TRIALS).

7.1.4 Geriatrics

Clinical studies of BAQSIMI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited clinical trial experience has not identified differences in responses between the elderly and younger patients.

7.1.5 Patients with type 2 diabetes

When deciding about the use of BAQSIMI for the patient with type 2 diabetes, consider those with a long duration of diabetes and/or insulin treatment. Those with advanced type 2 diabetes have a similar decline in counter-regulatory hormones as do those with type 1 diabetes.

BAQSIMI has not been studied for treatment of hypoglycemia in patients treated with sulfonylureas and should not be used in these patients (See Drug-Drug Interactions).

7.1.6 Use with alcohol

Alcohol can suppress hepatic gluconeogenesis and chronic alcoholism can deplete liver glycogen stores. Therefore BAQSIMI may be less effective in presence of acute or chronic alcohol ingestion.

7.1.7 Monitoring and Laboratory Tests

Blood glucose determinations should be obtained to follow the patient with hypoglycemia until the patient is asymptomatic.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of BAQSIMI has been assessed in 9 clinical studies in adult patients with and without diabetes mellitus, and 2 studies in pediatric patients (4 to <18 years of age) with diabetes mellitus.

The most common (≥10%) adverse reactions associated with BAQSIMI in adults were nausea, vomiting, headache, and upper respiratory tract irritation, which includes rhinorrhea, nasal discomfort, nasal congestion, cough, epistaxis and oropharyngeal pain. Adverse reactions were typically mild to moderate in severity and none were serious.

The adverse reactions were similar in adult and pediatric patients.

8.2 Clinical Trial Adverse Reactions (Adults)

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Two similarly designed comparator-controlled trials (IGBC and IGBI) evaluated the safety of a single 3 mg dose of BAQSIMI compared to a 1 mg dose of intra-muscular glucagon (IMG) in adult patients with diabetes. Table 2 provides a listing of the adverse reactions reported with a frequency of ≥2% in studies IGBC and IGBI.

Table 2: Adverse Reactions with an incidence ≥2% occurring in Adult Patients with Diabetes in Study IGBC and Study IGBI

Adverse Reaction System Organ Class Preferred Term	IGBC Type 1 and Type 2 Diabetes		IGBI Type 1 Diabetes	
	BAQSIMI 3 mg (n=83) %	IMG 1 mg (n=82) %	BAQSIMI 3 mg (n=70) %	IMG 1 mg (n=69) %
Ear and Labyrinth Disorders				
Ear pain	2.4	1.2	0	0
Eye Disorders				
Lacrimation increased	8.4	1.2	0	0
Eye pruritus	2.4	1.2	0	0
Gastrointestinal Disorders				
Nausea	21.7	26.8	31.4	42.0
Vomiting	15.7	11.0	14.3	17.4
General Disorders and Administration Site Conditions				
Fatigue	8.4	8.5	0	0
Facial pain	2.4	0	0	0
Infections and Infestations				
Nasopharyngitis	0	0	5.7	2.9

Musculoskeletal and Connective Tissue Disorders				
Muscular weakness	2.4	0	0	0
Nervous System Disorders				
Headache	20.5	8.5	15.7	10.1
Head discomfort	2.4	0	0	0
Somnolence	2.4	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Nasal discomfort	9.6	0	0	0
Nasal congestion	8.4	1.2	0	0
Rhinorrhea	2.4	1.2	0	0
Oropharyngeal pain	0	0	2.9	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.6	1.2	0	0

8.3 Clinical Trial Adverse Reactions (Pediatrics)

A single 3 mg dose of BAQSIMI was compared to weight based doses of 0.5 mg or 1 mg of IMG in pediatric patients with type 1 diabetes. Table 3 presents adverse reactions that occurred in the pediatric study IGBB at an incidence of ≥2%.

Table 3: Adverse Reactions with an Incidence ≥2% occurring in Pediatrics Patients with Type 1 Diabetes in Study IGBB

Adverse Reaction System Organ Class Preferred Term	IGBB Type 1 Diabetes	
	BAQSIMI 3 mg (n=36) %	IMG (weight based) (n=24) %
Eye Disorders		
Eye irritation	2.8	0
Ocular discomfort	2.8	0
Gastrointestinal Disorders		
Vomiting	30.6	37.5
Nausea	16.7	33.3
Abdominal pain upper	2.8	4.2
Diarrhea	0	4.2
General Disorders and Administration Site Conditions		
Injection site discomfort	0	20.8
Catheter site pain	0	4.2
Metabolism and Nutrition Disorders		
Hypoglycemia	0	4.2
Nervous System Disorders		
Headache	25.0	12.5
Dizziness	0	4.2

Respiratory, Thoracic, and Mediastinal Disorders		
Nasal discomfort	8.3	0
Nasal congestion	5.6	0
Sneezing	2.8	0

8.4 Less Common Clinical Trial Adverse Reactions

Other clinically relevant findings observed with BAQSIMI treated patients across clinical trials IGBC, IGBI and IGBB, were:

Cardiac Disorders: tachycardia
Eye Disorders: eye pain, ocular hyperemia
Gastrointestinal Disorders: abdominal discomfort
Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: neck pain
Nervous System Disorders: disturbance in attention
Psychiatric Disorders: anxiety, confusional state
Respiratory, Thoracic and Mediastinal Disorders: cough, epistaxis, nasal edema, upper-airway cough syndrome
Skin and Subcutaneous Tissue Disorders: hyperhidrosis

Clinically relevant findings observed across other clinical trials with BAQSIMI were:
Dysgeusia, nasal pruritus, hypertension, throat irritation, and parosmia.

8.5 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Vital Signs
Glucagon exerts positive inotropic and chronotropic effects and may, therefore, cause a temporary increase in both blood pressure and pulse rate.

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity.

In 3 clinical trials, 3/124 (2%) of BAQSIMI-treated patients had treatment-emergent anti-drug antibodies as detected by an affinity capture elution (ACE) ligand-binding immunogenicity assay. No neutralizing antibodies were detected.

9 DRUG INTERACTIONS

9.1 Overview

No formal drug-drug interactions studies were performed on BAQSIMI.

Published literature has shown the following interactions.

9.2 Drug-Drug Interactions

Beta-blockers: Patients taking beta-blockers might be expected to have a greater increase in both pulse and blood pressure when given glucagon, 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.

Indomethacin: When used with indomethacin, glucagon may lose its ability to raise blood glucose or may even produce hypoglycemia.

Insulin: Reacts antagonistically towards glucagon.

Sulfonylureas: The pharmacokinetic characteristics of sulfonylureas will result in remaining systemic concentrations for a long time and thus can cause significant and prolonged hypoglycemia. The preferred treatment of severe hypoglycemia in patients taking sulfonylureas is therefore the administration of glucose by IV bolus injection followed by continuous IV infusion until the end of the pharmacologic effects of the sulfonylureas. BAQSIMI has not been studied for treatment of hypoglycemia in patients treated with sulfonylureas and should not be used in these patients.

Warfarin: Glucagon may increase the anticoagulant effect of warfarin.

9.3 Drug-Food Interactions

Interactions with food have not been studied.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

9.6 Drug-Lifestyle Interactions

Interactions with lifestyle have not been studied.

Alcohol induced hypoglycemia is associated with a failure of blood glucose levels to rise normally after glucagon administration.

10 ACTION AND CLINICAL PHARMACOLOGY

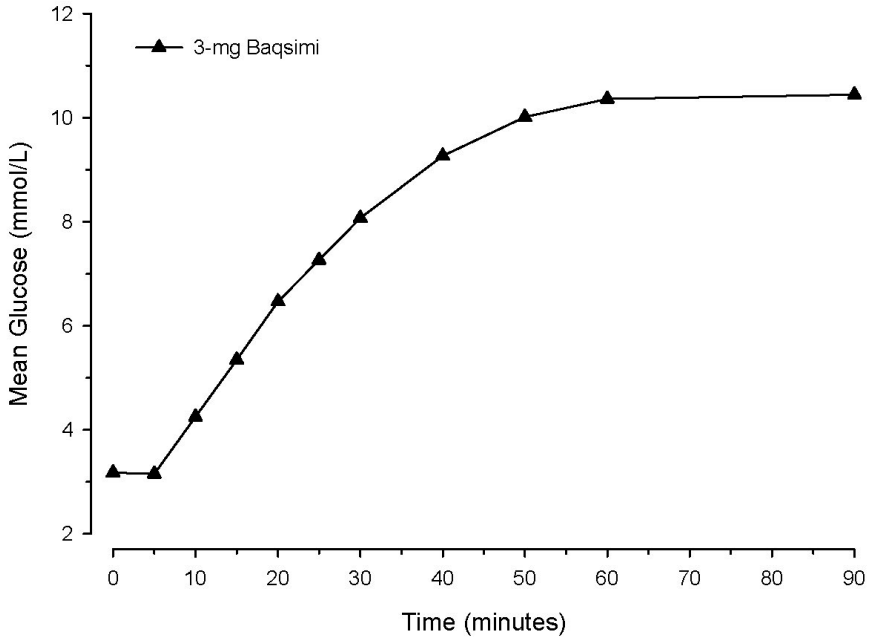
10.1 Mechanism of Action

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 antihypoglycemic effect.

10.2 Pharmacodynamics

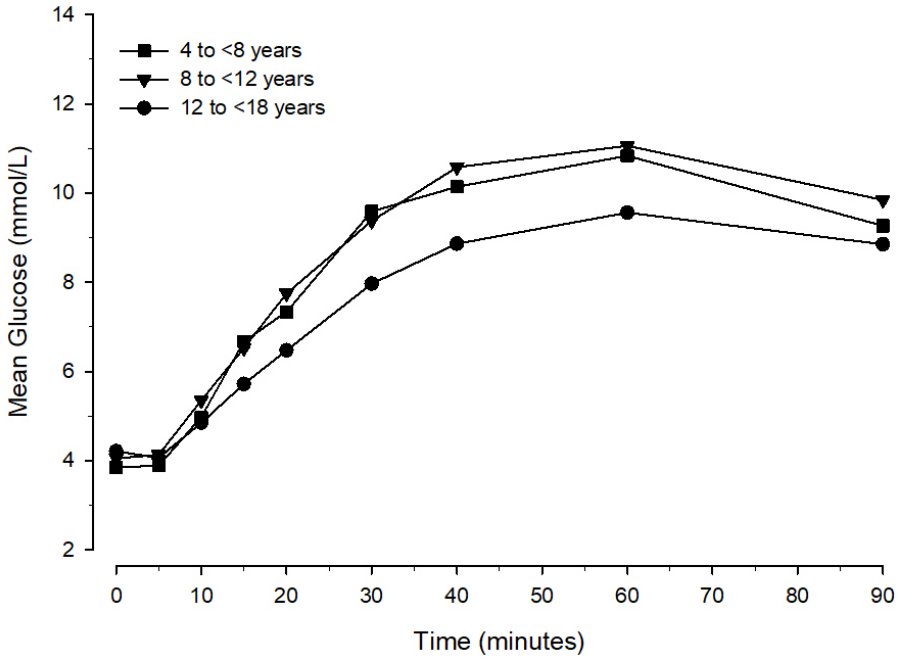
After administration of BAQSIMI in adult patients with type 1 diabetes the mean maximum glucose increase from baseline was 7.8 mmol/L as shown in Figure 1.

Figure 1 Mean glucose concentration over time in adult Type 1 Diabetes patients with insulin induced hypoglycemia treated with BAQSIMI.



In pediatric patients with type 1 diabetes (4 to <18 years), after administration of BAQSIMI, the mean maximum glucose increase from baseline was 7.6 mmol/L (4 to <8 years), 7.4 mmol/L (8 to <12 years), and 5.7 mmol/L (12 to <18 years), shown in Figure 2.

Figure 2 Mean glucose concentration over time in pediatric Type 1 Diabetes patients treated with BAQSIMI



Sex and body weight had no clinically meaningful effects on the pharmacodynamics of BAQSIMI.

Common cold with nasal congestion tested with or without use of decongestant did not impact pharmacodynamics of BAQSIMI.

10.3 Pharmacokinetics

Table 4: Summary of Glucagon Pharmacokinetic Parameters in Adult Type 1 Diabetes Patients Treated with BAQSIMI

	C_{max}	T_{max}[a]	$t_{1/2}$[a]	AUC_{0-4}	CL/F	Vd/F
Single dose geometric mean	6.1 ng/mL	0.25 h	0.585 h	2.7 ng*h/mL	981 L/h	885 L

[a] Median

Absorption: Glucagon absorption via the intranasal route, achieved mean peak plasma levels of 6.1 ng/mL at around 15 minutes.

Distribution: The apparent volume of distribution was approximately 885 L.

Metabolism: Glucagon is known to be degraded in the liver, kidneys, and plasma. Urinary excretion of intact glucagon has not been measured.

Elimination: The median half-life was approximately 35 minutes.

Special Populations and Conditions

Pediatrics: In pediatric patients (4 to <18 years), glucagon via the intranasal route achieved mean peak plasma levels between 15 and 20 minutes. The median half-life was 21 to 31 minutes.

Common Cold and Use of Decongestant: Common cold with nasal congestion or use of decongestant did not impact the pharmacokinetics of BAQSIMI.

11 STORAGE, STABILITY AND DISPOSAL

Store BAQSIMI in the shrink wrapped tube at temperatures up to 30ºC (86ºF).

Discard the used device and tube after use.

12 SPECIAL HANDLING INSTRUCTIONS

Keep BAQSIMI in the shrink wrapped tube until ready to use.

If the tube has been opened, BAQSIMI may have been exposed to moisture. This could cause BAQSIMI to not work as expected.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

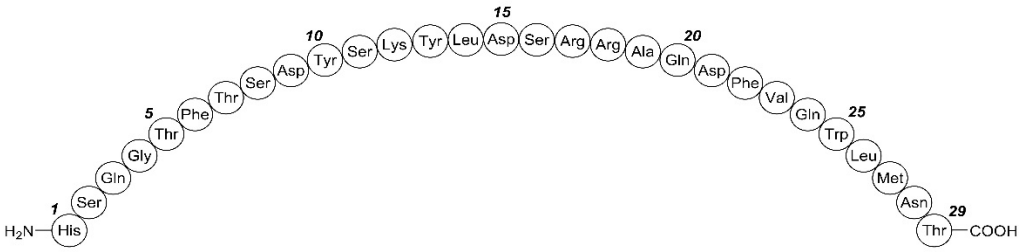
Drug Substance

Proper name: Glucagon

Chemical name: Glucagon

Molecular formula and molecular mass: The empirical formula is $C_{153}H_{225}N_{43}O_{49}S$ with a molecular weight of 3483.

Structural formula:



Physicochemical properties: Glucagon nasal powder is a preservative free, white powder.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 5: Summary of Trial Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Adult Study in patients with Type 1 and Type 2 Diabetes					
IGBC	Randomized, multicenter, open-label, 2-period, crossover study	Single 3 mg dose of BAQSIMI intranasally Or Single 1 mg dose of intra-muscular glucagon	Type 1 Diabetes n=77 Type 2 Diabetes n=6	Type 1 Diabetes 32.9 (18-64) years Type 2 Diabetes 47.8 (18-63) years	Type 1 Diabetes 58% Female 42% Male Type 2 Diabetes 67% Female 33% Male

Adult Study in patients with Type 1 Diabetes					
IGBI	Randomized, multicenter, open-label, 2-period, crossover study	Single 3 mg dose of BAQSIMI intranasally Or Single 1 mg dose of intra-muscular glucagon	Type 1 Diabetes n=70	41.7 (20-64) years	39% Female 61% Male
Pediatric Study in patients with Type 1 Diabetes					
IGBB	Randomized, multicenter, open-label, clinical study[a]	Single dose of BAQSIMI 3 mg intranasally[a] Or Single 0.5 or 1 mg dose of intra-muscular glucagon (based upon body weight)	Type 1 Diabetes n=18 n=18 n=12	Young children cohort 6.5 (4 to <8) years Children cohort 11.1 (8 to <12) years Adolescent cohort 14.6 (12 to <18) years	17% Female 83% Male 44% Female 56% Male 42% Female 58% Male

[a] Patients in the Young children and Children cohorts were randomly assigned 2:1 to receive single doses of BAQSIMI 2 mg and 3 mg in a crossover manner or a single dose weight-based intramuscular glucagon (0.5 or 1 mg). Patients in the Adolescent cohort were randomly assigned 1:1 to receive a single dose of BAQSIMI 3 mg and 1 mg intramuscular glucagon in a crossover manner. The 2 mg and 3 mg doses in Young children and Children cohorts were blinded; all other dosing was open-label.

Adult Patients:
Study IGBC was a randomized, multicenter, open-label, 2-period, crossover 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 BAQSIMI against a 1 mg dose of intra-muscular glucagon (IMG) in adult patients with type 1 diabetes. Insulin was used to reduce blood glucose levels to the hypoglycemic range with a target blood glucose nadir of <2.8 mmol/L. The primary efficacy outcome was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥3.9 mmol/L or an increase of ≥1.1 mmol/L 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.

Study IGBC enrolled 83 total patients 18 to 64 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 and 74 (96%) patients were white. The mean age of patients with T2D (N=6) was 47.8 years, with a mean diabetes duration of 18.8 years, 4 (67%) patients were female and 1 (17%) patient was white.

Study, IGBI was a randomized, multicenter, open-label, 2-period, crossover study in adult patients with type 1 diabetes. The efficacy of a single 3 mg dose of BAQSIMI was compared to a 1 mg dose of intra-muscular glucagon (IMG). Insulin was used to reduce blood glucose levels

to the hypoglycemic range with a target blood glucose nadir of <3.3 mmol/L. The primary efficacy outcome was identical to the primary efficacy outcome defined in Study IGBC. Seventy patients with type 1 diabetes were enrolled, with a mean age of 41.7 years and a mean diabetes duration of 19.8 years. Twenty-seven (39%) patients were female.

Pediatric Patients
Study IGBB was a randomized, multicenter, open-label clinical study that assessed BAQSIMI compared to intra-muscular glucagon (IMG) in pediatric patients aged 4 years and older with type 1 diabetes. Insulin was used to reduce blood glucose levels, and glucagon was administered after glucose reached <4.4 mmol/L on the dosing day. The primary objective was to assess the PK and PD of BAQSIMI compared to a weight-based dose of intra-muscular glucagon. Efficacy was assessed based on percentage of patients with a glucose increase of ≥1.1 mmol/L from glucose nadir within 30 minutes following glucagon administration.

Forty-eight patients were enrolled and received at least one dose of study drug. 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 Adolescent cohort (12 to <18 years) mean age was 14.6 years. In all age cohorts, the population was predominantly male and white.

14.2 Study Results

Adult Patients
Study IGBC in Adult Patients with Type 1 and Type 2 Diabetes
For patients with type 1 diabetes (n=75), the mean nadir blood glucose was 2.5 mmol/L for BAQSIMI and 2.7 mmol/L for IMG. BAQSIMI demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia with 98.7% of BAQSIMI-treated patients and 100% of IMG-treated patients achieving treatment success within 30 minutes. All patients met glucose treatment success criteria within 40 minutes. The mean time to treatment success, which did not include glucagon preparation time, for type 1 diabetes was 16.2 and 12.2 minutes in the BAQSIMI 3 mg and IMG 1 mg treatment groups, respectively. The difference in mean time to treatment success was statistically significant.

For patients with type 2 diabetes (n=5), the mean nadir blood glucose was 3.0 mmol/L for BAQSIMI and 2.9 mmol/L for IMG. All patients with type 2 diabetes (100%) achieved treatment success. The mean time to treatment success, which did not include glucagon preparation time, for type 2 diabetes was 11 and 10 minutes in the BAQSIMI and IMG 1 mg treatment groups, respectively.

Table 6: Patients Meeting Treatment Success and Other Glucose Criteria in Study IGBC

	Type 1 Diabetes (N=75)[a]		**Type 1 and Type 2 Diabetes (N=80)[a]**	
	BAQSIMI 3 mg	**IMG 1 mg**	**BAQSIMI 3 mg**	**IMG 1 mg**
Treatment Success – n (%)	74 (98.7%)	75 (100%)	79 (98.8%)	80 (100%)
Treatment Difference (1-sided upper 97.5% confidence limit) [b, c]	1.3% (4.0%)		1.3% (3.7%)	
Glucose criterion met – n (%)[d]				
(i) ≥3.9 mmol/L	72 (97%)	74 (99%)	77 (97%)	79 (99%)
(ii) Increase by ≥1.1 mmol/L 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 Drug with evaluable primary outcome.

[b] Difference calculated as (percentage with success in IMG) – (percentage with success in BAQSIMI).

[c] 1-sided confidence interval (CI) from a 1-sample mean of the paired differences in occurrence of outcome; non-inferiority margin = 10%.

[d] Percentage based on number of patients meeting treatment success.

Study IGBI in Adult Patients with Type 1 Diabetes

For the IGBI study the mean nadir blood glucose was 3.0 mmol/L for BAQSIMI and 3.1 mmol/L for IMG. BAQSIMI demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia with 100% of BAQSIMI-treated patients and 100% of IMG-treated patients achieving treatment success. All patients achieved both the pre-defined treatment success of an increased plasma glucose to ≥3.9 mmol/L and an increase in glucose of ≥1.1 mmol/L from nadir within 30 minutes after receiving BAQSIMI or IMG. The mean time to treatment success was 11.4 and 9.9 minutes in the BAQSIMI and IMG 1 mg treatment groups, respectively.

Pediatric Patients

Study IGBB in Pediatric Patients with Type 1 Diabetes

In study IGBB, across all age groups, BAQSIMI 3 mg and IMG 0.5 mg or 1 mg (based upon body weight), demonstrated similar glycemic responses. All (100%) patients in both treatment arms across all age groups achieved an increase in glucose ≥1.1 mmol/L from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase of ≥1.1 mmol/L is shown in Table 7 below.

Table 7: Mean Time to Reach Glucose Increase of ≥1.1 mmol/L from Nadir in Pediatric Study IGBB

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 <18 years old)	
	BAQSIMI 3 mg N=12	IMG[a] N=6	BAQSIMI 3 mg N=12	IMG[a] N=6	BAQSIMI 3 mg N=12	IMG[a] N=12
≥1.1 mmol/L	10.8	10.0	11.3	12.5	14.2	12.5

[a] 0.5 mg or 1 mg of IMG (based upon body weight)

15 NON-CLINICAL TOXICOLOGY

Repeat-Dose Toxicology

Rats were dosed by intranasal (IN) instillation with a solubilized formulation of nasal glucagon at 0.1 and 0.2 mg/rat/day (20.9- and 29.1-fold, respectively, the glucagon AUC in patients with diabetes following a 3 mg IN dose of nasal glucagon) for 28 consecutive days. Daily dosing over 28 days in rats was well tolerated; there were no nasal glucagon-related adverse effects on survival, clinical signs, body weights, food consumption, ophthalmoscopy, clinical pathology, or systemic anatomic pathology. Adverse effects were limited to local effects in the nasal cavity at the highest dose only (0.2 mg/day). Reversible mild to moderate erosion/ulceration of the olfactory epithelium occurred, frequently accompanied by minimal to mild, acute to subacute inflammation of the lamina propria at the dorsal turbinates of the nasal cavity in the 0.2 mg/day group. The placebo (15% DPC and 85% beta-cyclodextrin) produced no changes to the olfactory epithelia of rats after daily intranasal dosing for 28 days. The no-observed-adverse-effect level (NOAEL) for systemic target organ toxicity was considered to be 0.2 mg/day in rats (29.1-fold the human AUC following a 3 mg IN dose).

In dogs, the intended clinical nasal dosing device was used to administer the dry powder formulation of nasal glucagon at 2 and 4 mg/dog/day (139- and 194-fold, respectively, the glucagon AUC in patients with diabetes following a 3 mg IN dose of BAQSIMI) for 28 consecutive days. There were no test article-related adverse effects on body weight, food consumption, ophthalmology, electrocardiography, hematology, coagulation parameters, clinical chemistry, urinalysis, organ weights, or systemic anatomic pathology. With the exception of transient salivation and some sneezing in most dogs immediately after IN dosing, daily nasal glucagon dosing for 28 days was well tolerated. As in rats, adverse effects were limited to local effects in the nasal cavity. Microscopically, reversible mild to moderate atrophy/degeneration of the olfactory epithelium was observed in the nasal cavity of the placebo (15% DPC and 85% beta-cyclodextrin), 2 mg/day and 4 mg/day groups, with an increased incidence and severity in the nasal glucagon-treated dogs. The NOAEL for systemic target organ toxicity was considered to be 4 mg/day in dogs (194-fold the human AUC following a 3 mg IN dose).

Carcinogenicity

Because nasal glucagon is a single-use product indicated as rescue treatment for severe hypoglycemia, carcinogenicity studies have not been conducted.

Genotoxicity

Because nasal glucagon is a biotherapeutic peptide, no genetic toxicity studies were conducted.

DPC was not genotoxic in in vitro bacterial reverse mutation and chromosome aberration assays and the in vivo micronucleus assay in rats.

Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies have been conducted with nasal glucagon. Reproductive and developmental toxicology studies have been conducted previously with marketed recombinant glucagon products as well as animal-sourced glucagon products and revealed no evidence of harm to the fetus or impaired fertility. In addition, glucagon has been shown not to cross the human placenta further lowering the level of concern for potential fetal effects.

DPC did not adversely affect male or female reproductive performance or early embryonic development of rats dosed IV daily with up to 3 mg/kg/day prior to and throughout cohabitation until implantation (approximately 4 to 6 weeks, depending on gender).

DPC did not adversely affect embryo-fetal development in rats and rabbits dosed IV daily throughout organogenesis with up to 2.5 and 1 mg/kg/day, respectively.

DPC did not adversely affect maternal (F_0) growth and reproduction or offspring (F_1) growth, behaviour, and reproduction following daily IV doses up to 1 mg/kg/day to maternal rats from Gestation Day 6 through Postnatal Day 20.

Special Toxicology Studies

A single ocular instillation via powder dosing devices pre-filled with 30 mg nasal glucagon to male New Zealand White rabbits was well tolerated, with minimal ocular irritation limited to slight erythema and edema localized to the conjunctiva and palpebral membrane.

Juvenile Toxicology

No juvenile animal toxicology studies have been conducted with nasal glucagon.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

BAQSIMI®
glucagon nasal powder

Read this carefully before you start taking BAQSIMI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BAQSIMI.

Show your family and friends where you keep BAQSIMI and explain when and how to use it. They need to know how to use it before you need it. Each BAQSIMI device comes with a package leaflet. **Keep them together at all times.** The package leaflet contains **all** the information needed to correctly give and use BAQSIMI.

Serious Warnings and Precautions

BAQSIMI should only be given when the person is unable to swallow sugar such as candy or orange juice. After giving BAQSIMI call for medical help right away. Patients usually respond to BAQSIMI within 15 minutes. Wait for medical assistance. They may need to give the person glucose in their veins (intravenously). When the person responds, get them to eat as soon as they are able to safely swallow.

BAQSIMI will not help if the person does not have enough glucose stored in the liver. Intravenous (IV) glucose must be given in these cases. This can occur if they have:

- not been eating for a long time.
- an illness that prevents them from making enough hormones from the adrenal gland (called adrenal insufficiency).
- chronic low blood sugar.

What is BAQSIMI used for?

BAQSIMI is a medicine used to treat severe low blood sugar. This is called severe hypoglycemia. It is used in adults and children who are older than 4 that take insulin for diabetes. It is used when the person is unable to swallow sugar.

How does BAQSIMI work?

BAQSIMI helps to increase blood sugar. It does this by releasing stored glucose (glycogen) from the liver to the blood.

What are the ingredients in BAQSIMI?

Medicinal ingredients: glucagon
Non-medicinal ingredients: betadex and dodecylphosphocholine

BAQSIMI comes in the following dosage forms:

BAQSIMI is a **single use** device. It is only for use in the nose. Each device contains 3 mg of glucagon nasal powder.

BAQSIMI comes in both a single and a two pack. Each BAQSIMI device comes with a package leaflet. **Keep them together at all times.**

Do not use BAQSIMI if you:

- are allergic to glucagon, or to any of the other ingredients.
- have a tumor in the gland on top of your kidneys called the adrenal gland. This tumor is called pheochromocytoma.
- have a tumor in your pancreas called insulinoma.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BAQSIMI. Talk about any health conditions or problems you may have.

BAQSIMI may not work if the person does not have enough glucose stored in the liver. This can occur with fasting, chronic low blood sugar or underactive adrenal glands. BAQSIMI may not work if the person drinks too much alcohol.

Other warnings you should know about:

- Pregnant or plan to become pregnant. Talk with your doctor about the potential benefit for the mother. Decide if using BAQSIMI is justified based on the unknown risks to the mother and unborn baby.
- Breastfeeding or plan to breastfeed. It is not known if BAQSIMI passes into your breast milk.

Driving and using Machines:

If you have low blood sugar, your ability to concentrate and react may be impaired. After taking BAQSIMI you should wait until you know your blood sugar levels are in normal range before doing tasks. Low blood sugar can return after taking BAQSIMI.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BAQSIMI:

- beta-blockers
- indomethacin
- warfarin
- insulin
- sulfonylureas: these are drugs to treat patients with type 2 diabetes. It is not recommended to take BAQSIMI if you take this kind of drug.

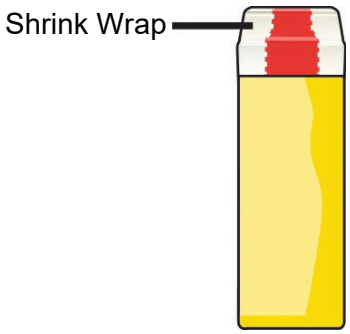
How to take BAQSIMI:

- Show your family and friends where you keep BAQSIMI and the package leaflet. Explain how to use it by sharing these instructions. **They need to know how to use it before you need it.**

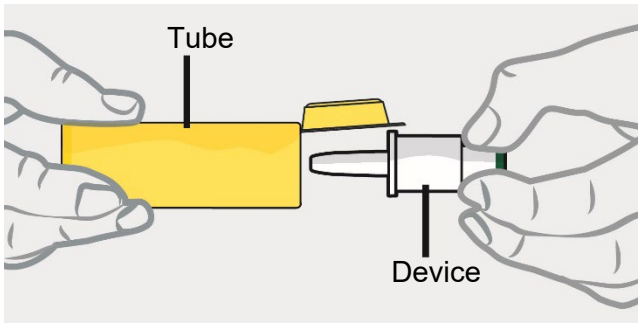
Important Points

- Keep BAQSIMI in the shrink wrapped Tube until ready to use.
- If the Tube has been opened, BAQSIMI may have been exposed to moisture. **This could cause BAQSIMI to not work as expected.**
- Each single device of BAQSIMI contains 1 dose of glucagon nasal powder and can only be used once. **Do not test before use.**
- Only use BAQSIMI in the nose.
- BAQSIMI will work even if you have a cold or are taking cold medicine.

Preparing the Dose

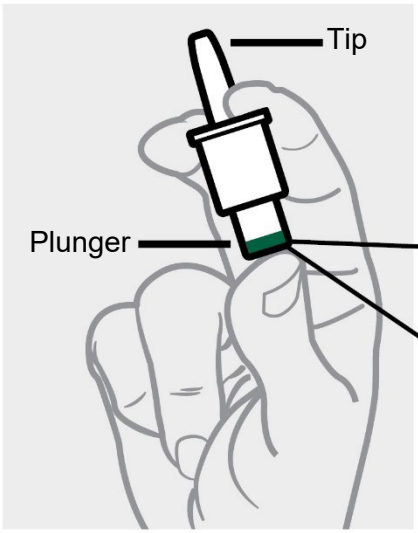


- Remove the Shrink Wrap by pulling on red stripe.



- Open the lid and remove the Device from the Tube.

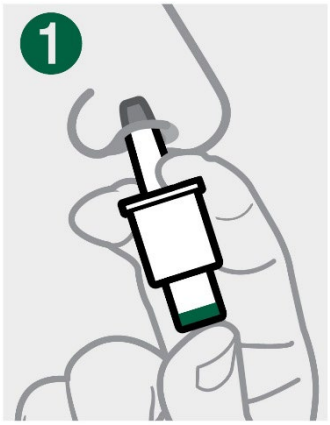
  Do not test before use.



- Hold the Device between fingers and thumb.

  Caution: Do not press the Plunger until ready to give the dose.

Giving the Dose



- Insert the Tip gently in one of the nostrils **until finger(s) touch the outside of the nose.**

- Push the Plunger all the way in.
- The dose is complete **when the Green Line is no longer showing**.

After Giving the Dose

- Remove the Tip from nose. **Throw away the used Device and Tube.**
- **Call for medical help right away.**
- If the person is unconscious, turn them on their side.
- Patients usually respond to BAQSIMI within 15 minutes. **Encourage the person to eat as soon as they can safely swallow.** Give the person a fast-acting source of sugar, such as juice or regular soda. Then give the person a long-acting source of sugar, such as crackers and cheese, peanut butter, or a meat sandwich.
- Tell your doctor each time you use BAQSIMI. Your doctor may need to adjust your dose of drugs for diabetes.

Caution: Replace the used BAQSIMI right away so you will have a new BAQSIMI in case you need it.

Usual adult and pediatric (4 years and older) dose:
3 mg given into one nostril (intranasal). Each device contains a single dose.

Overdose:

If you think you have taken too much BAQSIMI contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. They may include nausea, vomiting, diarrhea, or slowing down of your gut. An increase in blood pressure and pulse rate can also occur.

What are possible side effects from using BAQSIMI?

These are not all the possible side effects you may feel when taking BAQSIMI. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Nausea, vomiting, abdominal pain or discomfort
- Upper respiratory tract irritation which includes sneezing, runny or stuffy nose, nose bleed or discomfort, cough, sore throat
- Headache, weakness, fatigue, sleepiness
- Watery, red or itchy eyes
- Ear, face or neck pain
- Change in sense of taste or smell
- Lack of attention, confusion, anxiety
- Itchy skin, increased sweating
- Increased heart rate and blood pressure

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Allergic reaction (anaphylaxis):** wheezing or difficulty breathing or swallowing. Sweating, rash, hives, swollen face, lips, tongue, or throat. Rapid heartbeat, collapse and low blood pressure.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

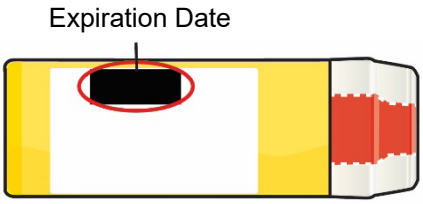
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store BAQSIMI in the shrink wrapped tube at temperatures up to 30°C (86°F).
- Only use BAQSIMI before the expiration date printed on the carton or tube.
- Replace BAQSIMI before the expiration date.



Keep out of reach and sight of children.

If you want more information about BAQSIMI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.amphastar.com, or by calling 1-800-423-4136.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

You may need to read this package leaflet again. Please do not throw it away until you have finished your medicine.

This leaflet was prepared by Amphastar Pharmaceuticals, Inc., 11570 6th Street, Rancho Cucamonga, CA 91730.

Last Revised: February 14, 2024

678351CAB/12-23