EU Risk Management Plan (Version 1.1)

Global Patient Safety
Signatory information is available on request.

Approval Date: May 19, 2025

EU Risk Management Plan for Baqsimi (Glucagon)

RMP version to be assessed as part of the application:

RMP version number: 1.1

Data lock point for this RMP: 24 July, 2024

Date of final sign off: See cover page of this document.

Rationale for submitting an updated RMP:

This RMP is submitted as part of the Type II Variation for paediatric age expansion from 4 to <17 years to 1 to < 17 years. The MAH changed from Eli Lilly to Amphastar France Pharmaceuticals with an effective date of 16 February 2024.

Summary of significant changes in this RMP:

Module/section	Description of major changes
Part I Product overview	Update of the population in the indication following extension of the paediatric population from 4 to <17 years to 1 to < 17 years. Transfer of MAH from Eli Lilly to Amphastar France Pharmaceuticals
Part II Safety Specification	
SI Epidemiology of the indication and target population(s)	Updated with data from the literature for the paediatric population, reference to current guidelines in children
SII Non-clinical part of the safety specification	N/A
SIII Clinical trial exposure	Update of exposure data up to 24th July 2024
SIV Populations not studied in clinical trials	N/A
SV Post-authorisation experience	Addition of post-authorisation data up to 24th July 2024
SVI Additional EU requirements for the safety specification	N/A
SVII Identified and potential risks	N/A
SVIII Summary of the safety concerns	N/A
Part III Pharmacovigilance Plan	N/A
Part IV Plan for post-authorisation efficacy studies	N/A
Part V Risk Minimisation Measures	N/A
Part VI Summary of RMP	Update of the population (from 1 year old) in section I The Medicine and What It is Used for In Part VI section "II.A List of Important Risks and Missing Information", the paragraph "Important risks of Baqsimi are risks…" has been reinstated to its previous position above the "II.A List of Important Risks and Missing Information" table. This change was made as per agency request.
Part VII Annexes	
[redacted]	[redacted]

Module/section	Description of major changes
[redacted]	[redacted]
ANNEX 4 Specific adverse drug reaction follow-up forms	Change the name of the follow up form: Specific Adverse Drug Reaction Baqsimi Follow-up Questionnaire (Reference AMP [redacted])
[redacted]	[redacted]
ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	N/A
ANNEX 7 Other supporting data (including referenced material)	Addition of new references per revisions to Part II, Module SI
[redacted]	[redacted]

Other RMP versions under evaluation:

RMP version number: Not applicable

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Details of the currently approved RMP:

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

Table of content

Part I: Product Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Glucagon
Pharmacotherapeutic group(s) (ATC Code)	H04AA01
Marketing Authorisation Applicant	Amphastar France Pharmaceuticals
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Baqsimi
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Synthetic polypeptide hormone
	Summary of mode 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 antihypoglycaemic effect.
	Important information about its composition: Glucagon nasal powder contains 3 mg of glucagon in a ready-to-use, single-use intranasal powder delivery device. Glucagon comprises 10% by weight of the powder in the device. The formulation also contains beta-cyclodextrin as a filler/bulking agent/absorption enhancer and dodecylphosphocholine (DPC) as an absorption enhancer/surfactant. Beta-cyclodextrin is a compendial excipient and DPC is a novel excipient.
Hyperlink to the Product Information	See Module 1.3.1
Indication(s) in the EEA	**Current:** Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus
	Proposed: Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 1 year and over with diabetes mellitus.
Dosage in the EEA	**Current:** A single 3-mg dose
	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current::** 3 mg synthetic glucagon nasal powder in a single-dose, prefilled dosing device.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Names; RMP = risk management plan.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Severe Hypoglycaemia

Hypoglycaemia is characterized by a low glucose plasma concentration. It is common in patients with diabetes mellitus due to an imbalance between food intake and insulin injections. Severe hypoglycaemia refers to an episode of hypoglycaemia that causes neurological impairment exposing the individual to potential harm and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions.

Plasma glucose concentrations may not be available during a severe event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (Seaquist et al. 2013). A blood glucose level of <54 mg/dL (<3.0 mmol/L) is considered as clinically significant hypoglycaemia or major hypoglycaemia due to the increased risk of injury or death for patients (IHSG 2017, Abraham et al., 2022).

In addition to accidents and physical injury, the morbidity of hypoglycaemia involves the cardiovascular and central nervous systems. Coma and seizures are well-recognized neurological sequelae of hypoglycaemia. It could also cause dangerous and life-threatening cardiac complications, such as arrhythmias and myocardial ischaemia, and permanent cognitive impairment or promote cognitive decline and accelerate the onset of dementia (Frier 2014).

Symptoms of hypoglycemia vary among patients according to age and diabetes duration. Children may demonstrate emotional and behavioral changes secondary to hypoglycemia in addition to classic autonomic and neuroglycopenic symptoms.

SI.1.1 Incidence

Hypoglycaemia occurs about 2 to 3 times more frequently in patients with type 1 diabetes mellitus (T1D) than in patients with type 2 diabetes mellitus (T2D) treated with insulin, and the incidence increases with age and the years of duration of diabetes (Donnelly et al. 2005; UKHSG 2007; Frier 2014). Because T2D is more prevalent than T1D, most episodes of hypoglycaemia (including severe) occur in people with T2D (Cryer 2008). The severity of hypoglycaemia is classified according to the patient's ability to self-treat (Seaquist et al. 2013). Mild hypoglycaemia episodes, where symptoms are self-recognised and self-treated, are reported as frequently as 1.6 to 1.8 events per week in people with T1D and 0.4 to 0.7 events per week in people with T2D (Frier 2014).

Severe hypoglycaemic events are reported in patients with T1D at a frequency of 30 to 320 events per 100 patient-years, and in insulin-treated patients with T2D, at a frequency of 10 to 80 events per 100 patient-years (Frier 2014; Edridge et al. 2015).

A decreasing trend with time was observed in a cohort of children and adolescents in Germany and Australia, with an incidence of 20.7 events of severe hypoglycemia and coma per 100 patient-years in 1995 and 3.6 per 100 patient-years in 2012. During the entire observation period, older age was associated with moderately decreased risk of severe hypoglycemia (6% risk reduction per 1-y age increase) and hypoglycemic coma (3% risk reduction per 1-y age increase) (Karges et al. 2014).

SI.1.2 Prevalence

The annual prevalence of severe hypoglycaemia in adult patients with T1D is approximately 30% (range 22% to 46%) (Frier 2014). The prevalence is lower in adults with insulin-treated T2D, affecting 7% to 25% of these patients (Frier 2014).

The annual prevalence of severe hypoglycemia in children with diabetes varies but has generally decreased over the past few decades due to advancements in diabetes management. The incidence of severe hypoglycemia in children with type 1 diabetes ranges from 1.21 to 30 events per 100 person-years (Coolen et al. 2021). The prevalence of severe hypoglycemia in children with type 1 diabetes in the EU also varies, but studies indicate a range of 5 to 20 events per 100 patient-years (Hill et al. 2023). This variation is due to differences in healthcare systems, diabetes management practices, and patient populations across different countries.

A meta-analysis for the prevalence of severe hypoglycaemia in patients with T2D showed a pooled prevalence of 6%, with a prevalence of 21% for insulin-treated patients (Edridge et al. 2015).

SI.1.3 Demographics of the Population in the Proposed Indication – (Age, Gender, Racial and/or Ethnic Origin) and Risk Factors for the Disease

Patients with T1D aged >60 years report an incidence of severe hypoglycaemia almost 2-fold higher than patients aged ≤60 years (40.1 vs. 24.3 events per 100 patient-years) (Schütt et al. 2012). Additionally, many studies of the prevalence of severe hypoglycaemia in the paediatric population have shown a correlation with younger age (Matyka 2014).
In paediatric patients evaluated in a real-life setting in Finland (data collected from 2018 to 2021), the average occurrence of serious hypoglycemic events per day was 0.32±0.04 in patient treated with multiple daily injections and 0.34±0.03 in those with continuous subcutaneous insulin infusion. Patients with an HbA1c ≤48mmol/mol showed increased total number of hypoglycemic events. However, there was no increase in the occurrence of serious hypoglycemic events (Hill et al. 2023).

Several risk factors for severe hypoglycaemia are reported in the literature, including duration of diabetes in patients with T1D (Pedersen-Bjergaard et al. 2004), and, in patients with T2D, the duration of treatment with insulin (UKHSG 2007). Intensive glycaemic control is associated with an increased risk of severe hypoglycaemia in patients with T1D (DCCT 1993; DCCT 1997) and T2D (ACCORD 2008; ADVANCE 2008).

Sleep is also an important risk factor for severe hypoglycaemia, with approximately 50% of all

episodes of severe hypoglycaemia occurring during sleep (DCCT 1991; Allen and Frier 2003). Impaired awareness of hypoglycaemia is observed in more patients with T1D than T2D, and is associated with an increased risk of severe hypoglycaemia (Strachan 2014; Schopman et al. 2010). In addition, several studies have shown female (Sämann et al. 2013; Giorda et al. 2015) and African American (Lipska et al. 2014; Karter et al. 2017; Lee et al. 2017) patients have an increased risk of experiencing severe hypoglycaemia, as compared to male and non-Hispanic White patients, respectively.

SI.1.4 Main Existing Treatment Options

Currently available treatments for severe hypoglycaemia were limited to intravenous (IV) dextrose and injectable glucagon. Intravenous dextrose requires administration by trained personnel within a hospital or emergency medical setting. The treatment of severe hypoglycaemia outside the hospital setting was mainly limited to injectable glucagon. Injectable glucagon products have been used clinically to treat severe hypoglycaemia for more than 50 years, and the benefits and risks associated with these products are well established. Injectable glucagon is currently not available in a ready-to-use formulation. Glucagon is unstable in the aqueous state (Onoue et al. 2006); therefore, the glucagon powder in glucagon emergency kits must be reconstituted using a multiple-step process before the drug can be administered to the patient by either subcutaneous or intramuscular injection.
Use of an intranasal needle-free device that delivers glucagon powder is a new recently approved easy to use option for the effective management of severe hypoglycaemia in patients with diabetes.

SI.1.5 Natural History of the Indicated Condition in the untreated Population, Including Mortality and Morbidity

Hypoglycaemia has serious clinical implications for patients with T1D or T2D and can also be life-threatening. Neuroglycopenia, resulting from hypoglycaemia, causes cognitive impairment, as well as changes in mood, and can lead to more serious consequences, including behavioural changes, loss of consciousness, seizures, coma, and even death (Cryer 2008); Whitmer et al. 2009; McCoy et al. 2012). Cognitive impairment can have other adverse outcomes, such as falls, fractures, or motor vehicle accidents (Frier 2014; Signorovitch 2013). Evidence also suggests that hypoglycaemia is associated with serious cardiac complications, such as arrhythmias (Chow et al. 2014; Pistrosch et al. 2015; Novodvorsky et al. 2017) and increased risk of death in critically ill patients (NICE-SUGAR 2012). Based upon recent reports of mortality rates, it is estimated that 4% to 10% of all deaths in patients with T1D can be attributed to hypoglycaemia (Seaquist et al. 2013).

In addition to acute, short-term implications, hypoglycaemia can negatively influence quality of life by interfering with employment, personal relationships, and other activities, and may be associated with onset or acceleration of dementia or cognitive decline. In addition, fear of or avoidance of hypoglycaemia can become a major barrier to optimal glycaemic control (Frier 2014).

SI.1.6 Important Co-morbidities

Patients with T1D are at increased risk of developing other autoimmune disorders, such as autoimmune thyroid disease, Addison's disease, celiac disease, and vitiligo (Kahaly and Hansen 2016). Celiac disease is more common among patients with T1D than among patients with T2D (Kylökäs et al. 2016). The prevalence of celiac disease among patients with T1D ranges from 4% to 9% (Kahaly and Hansen 2016), with a prevalence of 3% to 16% reported in children with T1D (Hagopian et al. 2017). Diabetic patients are more susceptible to thyroid disorders; the prevalence of thyroid disease was reported to be 10.8% among a community population of diabetic patients and up to 13.4% in a hospital diabetic clinic (Witting et al. 2014). Among patients with celiac disease, those with diabetes (type 1 or 2) had an increased risk of thyroid disease (Kylökäs et al. 2016). Pathological conditions associated with polyendocrine syndrome type 1 include T1D and Addison's disease (Cutolo 2014).

Approximately 0.5% of patients with diabetes are also diagnosed with Addison's disease and 2% to 10% experience vitiligo (Kahaly and Hansen 2016).

The literature describes the most common cause of chronic kidney disease worldwide as diabetes (Afkarian et al. 2016), and the prevalence of both conditions are on the rise (Thomas et al. 2016).

Diabetes can lead to end-stage renal disease as well as cardiovascular disease (Afkarian et al. 2016). Patients with diabetic dyslipidaemia are at an increased risk of cardiovascular morbidity and mortality, and the prevalence of dyslipidaemia among diabetic patients has been reported as high as 95% (Rajput et al. 2015). The prevalence of non-alcoholic fatty liver disease among patients with T2D is known to be high, and has been reported to be as high as 66% (Ballestri et al. 2016; Giorda et al. 2017). The prevalence has been increasing over time, and is thought to be related to an increase in insulin-resistance conditions, such as obesity, the metabolic syndrome, and diabetes (Giorda et al. 2017).

Module SII - Nonclinical Part of the Safety Specification

SII.1 Toxicity

Nasal glucagon is a novel, ready-to-use, single-use, nasal dosing device containing a glucagon powder formulation. The proposed indication of nasal glucagon is for the treatment of severe hypoglycaemia in adult and paediatric patients with diabetes mellitus. Thus, it is anticipated that this product will be used infrequently.

The active medicinal ingredient is synthetic glucagon, which is identical in amino acid sequence to human glucagon, and is supplied as a dry powder. Nasal glucagon drug product contains [redacted] synthetic glucagon + [redacted] dodecylphosphocholine (DPC) + [redacted] beta-cyclodextrin (β-CD), in a [redacted] (w/w/w), respectively.

The safety pharmacology and toxicology programme for nasal glucagon included 1-month repeat-dose studies in rats and dogs with the drug product (that is, combination of synthetic glucagon and excipients β-CD and DPC) selected for clinical studies. These studies were done to assess the safety of the drug product when given by the intranasal (IN) route of administration.

Beta-cyclodextrin has been used globally in food and pharmaceutical products for many years, although its use in the United States has been more limited than in Japan and Europe. For these reasons, no stand-alone toxicology studies were conducted with β-CD. However, β-CD was evaluated in the 28-day IN toxicity studies in rats and dogs as part of the Placebo Control Powder along with the third ingredient, the novel excipient, DPC. Beta-cyclodextrin also served as the reference agent for safety pharmacology assessments of respiratory and central nervous system (CNS) function.

For DPC, a series of safety pharmacology, genotoxicity, and reproduction studies, developed in accordance with recommendations from global regulatory authorities, was conducted to evaluate the safety profile.

Important findings and conclusions from the safety pharmacology and toxicology programme for nasal glucagon were:

- Nasal glucagon was well-tolerated in both rats and dogs dosed IN daily for 28 days.
- Reversible, local irritation of the olfactory epithelia was produced in the nasal cavity of rats ([redacted] glucagon/rat/day) and dogs ([redacted] glucagon/dog/day) after daily IN dosing with nasal glucagon for 28 days followed by a 14-day recovery phase. Minimal irritation was produced in the excipient only control groups, thus indicating the primary nasal irritant in nasal glucagon is synthetic glucagon.
- There was no evidence of systemic target organ toxicity in rats or dogs after daily IN dosing with nasal glucagon for 28 days. The no-observed-adverse-effect levels (NOAELs) were [redacted] synthetic glucagon/rat/day and [redacted] synthetic glucagon/dog/day, corresponding to glucagon plasma area under the concentration versus time curve-(AUC-)based exposure multiples of [redacted] and [redacted] the human AUC following a

therapeutic dose of nasal glucagon.

- Using the intended clinical single-use nasal dosing device, a [redacted] dose of nasal glucagon was distributed in the nasal passages, the nasopharynx, stomach, oesophagus, and on the tongue of dogs, as indicated by a blue powder tracer dye. There was no evidence of dye in the larynx or trachea, indicating that nasal glucagon did not distribute to the lung. Local nasal changes were limited to minimal inflammation, but no atrophy/degeneration of the olfactory epithelia was observed as was the case in the 28-day toxicity study in dogs.
- A single intratracheal insufflation of [redacted] nasal glucagon was well tolerated by rats. There were no nasal glucagon-related, abnormal gross pathology or histopathological findings in any animals necropsied the day after treatment or after the 14-day recovery phase.
- A single ocular instillation with the clinical single-use nasal dosing device prefilled with [redacted] nasal glucagon to male New Zealand White rabbits was well tolerated, with minimal ocular irritation limited to slight erythaema and oedema localised to the conjunctiva and palpebral membrane.

SII.2 Safety Pharmacology

Nasal glucagon ([redacted] glucagon/dog/day) did not produce adverse changes in heart rate (HR) or qualitative/quantitative electrocardiogram (ECG) parameters in a 28-day study in dogs.

SII.3 Other Toxicity-Related Information or Data

Important findings and conclusions from the safety pharmacology and toxicology studies of the novel excipient DPC were:

- DPC [redacted] was associated with a non-adverse, mild, transient, and reversible increase in arterial blood pressure in dogs, but there were no changes to qualitative or quantitative ECG parameters.
- DPC [redacted] produced a slight increase in respiratory rate and minute volume at 16 minutes post dose, but no adverse neurological effects.
- DPC given IN to dogs for 5 consecutive days at up to [redacted] was well tolerated and did not cause any adverse clinical signs or gross pathological changes at necropsy. Histologically, minimal inflammation and mild accumulation of basophilic material was noted in the nasal cavity, but there was no evidence of atrophy/degeneration of the olfactory epithelia.
- DPC was not genotoxic in in vitro bacterial reverse mutation [redacted] or chromosome aberration [redacted] assays or the in vivo micronucleus assay in rats [redacted].
- DPC did not adversely affect male or female reproductive performance or early embryonic development of rats dosed IV daily with up to [redacted] prior to and throughout cohabitation until implantation (approximately 4 to 6 weeks, depending on gender).
- DPC did not adversely affect embryo-foetal development in rats and rabbits dosed IV

daily throughout organogenesis with up to [redacted], respectively.

- DPC did not adversely affect maternal (F0) growth and reproduction or offspring (F1) growth, behaviour, and reproduction following daily IV doses up to
- [redacted] to maternal rats on gestation Day 6 through postnatal Day 20.

Module SIII - Clinical Trial Exposure

Nasal glucagon is not intended for chronic administration. Although approximately some of the of patients in the nasal glucagon development programme received more than 1 dose (range of 2 to 11 doses), no patients received daily or continuous dosing. Therefore, exposure is presented using only the number of patients, without person-time adjustment.

Cumulatively, 52 healthy volunteers (Phase 1) and 487 adult and paediatric patients have received nasal glucagon in clinical trials.

Table SIII.1. Cumulative Exposure in Nasal Glucagon Clinical Trials

Treatment	Number of Participants
Nasal glucagon	539
Comparator	304

[a] Includes participants who have received nasal glucagon and comparator in crossover trials and placebo lead- in trials. These patients are counted in each of the relevant groups.

Table SIII.2. Exposure to Nasal Glucagon by Age Group and Gender

Age Group	Male	Female	Total
<4 years	4	3	7
≥4 years and <8 years	11	6	17
≥8 years and <12 years	10	7	17
≥12 years and <18 years	13	11	24
≥18 years and <65 years	254	193	447
≥65 years	17	10	27
Total	**309**	**230**	**539**

Table SIII.3. Exposure to Nasal Glucagon by Dose

Dose of Exposure	Adult Patients (≥18 years)	Paediatric Patients (<18 years)	Total
0.5 mg	15	0	15
1 mg	26	0	26
2 mg	34	23	57
3 mg	434	65	499
6 mg	41	0	41
Total[a]	**474**	**65**	**539**

[a] The number of patients in the total row is not the sum of each column because a patient may have received different doses of nasal glucagon, but is only counted once in the total.

Table SIII.4. Exposure to Nasal Glucagon by Ethnic Origin

Ethnic Origin	Patients
Asian	75
Black	18
Caucasian	435
Other	11
Total	**539**

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion: Patients ≥65 years of age

Reason for exclusion: Patients aged ≥65 years were excluded from participation in the adult pivotal clinical trial because insulin was used to induce hypoglycaemia with a blood glucose target <50 mg/dL. Because many elderly patients have comorbidities (e.g., cardiovascular disease), they were excluded due to safety considerations.

Is it considered to be included as missing information?: No

Rationale: Glucagon has a well-established safety profile based on more than 50 years of clinical use. There is no reported clinical experience that has identified any difference in the safety profile of marketed glucagon products for this patient subgroup.

Only limited number of 27 patients with age ≥65 years of age have been exposed to nasal glucagon in clinical trial settings throughout the overall product development program, namely in the supportive studies I8R-MC-IGBF, I8R-MC-IGBG and I8R-MC-IGBH and the actual-use study I8R-MC-B002.

Criterion: Women who are pregnant

Reason for exclusion: This is a standard exclusion criterion in clinical development. Insufficient information on the effects of nasal glucagon on maternal health prohibited inclusion of pregnant women in the development programme. There were no pregnancies reported during the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: There are no documented safety concerns in this population for the currently marketed glucagon therapies. Nasal glucagon is identical to the endogenous hormone and does not cross the human placental barrier; therefore, no reproductive and developmental toxicity studies of nasal glucagon were conducted in animals. Reproduction studies conducted in rats and rabbits with animal-sourced glucagon have revealed no harm to the foetus. In addition, reproduction studies conducted in rats and rabbits with the DPC excipient have revealed no harm to the foetus.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure .

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SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin	See Module SIII; 19% of clinical trial participants had an ethnic origin other than Caucasian
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

Nasal glucagon was approved in the US on July 24, 2019. Since then it has been granted marketing authorization in 45 countries. The MAH voluntarily withdraw market authorization from 5 countries (Isreal, India, Bahrain, Oman and Saudi) due to commercial reason. At the time of this RMP, nasal glucagon has been authorized in 40 countries including those in the EU, US, Canada, Japan, and Switzerland.

Worldwide sales data of nasal glucagon have been collected for the time period of 25 July 2023 through 24 July 2024 and for the cumulative time period ending on 24 July 2024.

As sales data are only available in complete months, the data are reflective of the 1-Year period from 01 August 2023 through 31 July 2024 and the cumulative time frame ending on 31 July 2024.

During the period from 01 August 2023 through 31 July 2024, approximately 3,087,009 mg of nasal glucagon were sold worldwide. Considering use by 3 mg doses, this translates to approximately 1,029,003 mg intranasal doses of nasal glucagon. nasal glucagon is sold for use as required, the exposure data provided is based on sales during the reporting period. As nasal glucagon is an emergency use product, most patients will not be exposed to the product in the same reporting period in which they received the product.

SV.1.1 Method Used to Calculate Exposure

Worldwide sales data

SV.1.2 Exposure

Table SV.1 provides a geographical summary of worldwide sales and patient exposure.

Table SV.1 Estimated Post-Marketing Exposure to Nasal Glucagon

Region	Sales Ex-factory (Milligrams)	Patient exposure estimate
Europe	1,322,532	440,844
Japan	69,945	23,315
US	1,346,310	448,770
Other countries	348,222	116,074
Grand total	**3,087,009**	**1,029,003**

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No potential for misuse of nasal glucagon for illegal purposes has been observed in completed clinical trials. Furthermore, glucagon's mechanism of action and pharmacology do not suggest the potential for abuse or misuse.

It is not possible to predict the extent to which nasal glucagon may be misused, diverted, and/or abused once marketed on the basis of limited experience. However, the potential is considered to be negligible.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Serious hypersensitivity

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1:

None.

Risk-Benefit Impact:

Not applicable.

Important Potential Risk 1:

Inappropriate use of the device leading to loss of drug benefit

Risk-Benefit Impact:

Lack of drug benefit is a possibility for all medications, including the use of nasal glucagon in the emergency rescue of severe hypoglycaemia. Such events could result in outcomes sufficient to impact the benefit-risk, depending on the specific circumstances.

Of particular concern for nasal glucagon, is the possibility that the user of the nasal glucagon device fails to follow the instructions for use properly and thus, does not administer the medication to the severely hypoglycaemic patient.

Instructions for use, product labelling, and product packaging language have been developed to inform and educate healthcare providers, patients, and users on the proper use of the nasal glucagon device.

Missing Information 1:

None

Risk-Benefit Impact:

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: None

Important Potential Risk:
Inappropriate use of the device leading to loss of drug benefit

Potential mechanisms:

The user of the device could fail to follow the instructions for use and fail to administer the medication properly. This could result in a lack of drug benefit during severe hypoglycaemic event.

Evidence source(s) and strength of evidence:

In an emergency setting, the first-time user who is not familiar with the device or its instructions for use may fail to administer the medication correctly to the patient.

Characterisation of the risk:

In randomized, clinical trials of nasal glucagon, all device users were healthcare professionals who were trained on the proper use of the device; therefore, inappropriate use of the device did not occur in this setting.

Risk factors and risk groups:

Risk groups for inappropriate use of the device are likely to be first-time users who are unfamiliar with the device and the instructions for use.

Preventability:

Nasal glucagon instructions for use, product packaging and labelling describe the proper use of the device product.

Furthermore, additional risk minimisation measures in the form of educational materials have been proposed as described in Part V of this RMP.

Impact on the risk-benefit balance of the product:

The indication for use of nasal glucagon, severe hypoglycaemia, is a serious and potentially life-

threatening condition. In the clinical programme, nasal glucagon produced rapid increase in blood glucose levels and has demonstrated noninferiority to the commercially available intramuscular glucagon in reversing insulin-induced hypoglycaemia in patients with diabetes.

Nasal glucagon instructions for use, product packaging and labelling describe the proper use of the device product. Additional risk minimisation measures of administration leaflet, instructional video, and demonstration kit have been developed to further instruct the administration of nasal glucagon.

In addition, once nasal glucagon has been administered, caregivers are instructed in the product labelling materials, patient leaflet, and in instructions for use to call for immediate medical assistance. Therefore, if instances of inappropriate device use occur in the postmarketing experience, it will not likely impact the risk-benefit balance, provided that the frequency is low and the current standard of care for treatment of severe hypoglycaemia is maintained.

Public health impact:

Given that emergency medical assistance is the current standard of care for treatment of severe hypoglycaemia and will continue to be the standard of care after the introduction of nasal glucagon into the treatment paradigm, the impact on public health of inappropriate use of the nasal glucagon device is considered low.

SVII.3.2 Presentation of the Missing Information

Missing Information:

None.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Inappropriate use of the device leading to loss of drug benefit
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for Inappropriate use of the device leading to loss of drug benefit: [redacted].

Nasal glucagon adverse event follow-up form—to further characterize nasal glucagon device user behaviours associated with reported lack of drug benefit events

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) **Status** (planned/ongoing)	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Inappropriate use of the device leading to loss of drug benefit	Routine risk communication: SmPC Sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal and other handling), PL Section 3 (How Baqsimi is to be given), and IFU (Important Points to Know and Preparing the Dose) Routine risk minimisation activities recommending specific clinical measures to address the risk: Instructions for patients to discuss the proper use of glucagon with family and friends before it is needed—PL Section 2 (What you need to know before you receive Baqsimi) and IFU Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How Baqsimi is to be given), and IFU (After giving the dose). Other routine risk minimisation measures beyond the Product Information: Instructions for proper use are highlighted on the outer carton and tube container to state 'Do not press the plunger prior to insertion as you will lose the dose' and 'Do not press plunger before insertion', respectively. Pack size: Not applicable Legal status: Prescription only medicine

Abbreviations: IFU = Instructions for Use; PL = package leaflet; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Additional risk minimisation materials will be available at launch to healthcare professionals (HCPs) who are expected to prescribe and/or supply Baqsimi in order to train patients and/or caregivers upon initial Baqsimi prescription.

The risk minimisation materials are as follows:

- Administration leaflet
- Online instructional video
- Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device

Objectives:

Healthcare professionals who are expected to prescribe and/or supply Baqsimi will use the

additional risk minimisation materials to train patients and/or caregivers upon initial Baqsimi prescription. This will enable communication of important information to patients and/or caregivers to support their understanding and confidence on the correct handling and administration of Baqsimi.

Risk addressed:

- Inappropriate use of the device leading to loss of drug benefit

Rationale for the additional risk minimisation activity:

The administration leaflet, the online instructional video, and the demonstration kit that includes a trainer device with an administration leaflet will support the efforts of HCPs who are expected to prescribe and/or supply Baqsimi in order to educate patients and/or caregivers on the safe use of Baqsimi at the time of initial prescription.

Target audience and planned distribution path:

The target audience will be HCPs who are expected to prescribe and/or supply Baqsimi who will train patients and/or caregivers upon initial Baqsimi prescription. The planned distribution path of the risk minimisation materials will be agreed upon by each individual Member State.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable. Routine pharmacovigilance activities will be utilised to evaluate the risk of inappropriate use of the device leading to the loss of drug benefit.

Removal of additional risk minimisation activities:

Not applicable.

Removal of additional risk minimisation activities:

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Inappropriate use of the device leading to loss of drug benefit	Routine risk minimisation measures: SmPC Sections 4.2 (Posology and method of administration) and 6.6 (Special precaution for disposal and other handling), PL Section 3 (How Baqsimi is to be given), and IFU (Important points to know and preparing the dose). Routine risk minimisation activities recommending specific clinical measures to address the risk: Instructions for patients to discuss the proper use of glucagon with family and friends before it is needed—PL Section 2 (What you need to know before you receive Baqsimi) and IFU (Initial statement). Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How Baqsimi is to be given), and IFU (After giving the dose). Other routine risk minimisation measures beyond the Product Information: Instructions for proper use are highlighted on the device carton and tube container to state 'Do not press the plunger prior to insertion as you will lose the dose' and 'Do not press plunger before insertion', respectively. Additional risk minimisation measures: • Administration leaflet • Online instructional video • Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Nasal glucagon adverse event follow-up form Additional pharmacovigilance activities: Not applicable

Abbreviations: IFU = Instructions for Use; PL = package leaflet; SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Baqsimi (Glucagon)

This is a summary of the risk management plan (RMP) for Baqsimi. The RMP details important risks of Baqsimi, how these risks can be minimised, and how more information will be obtained about Baqsimi's risks.

Baqsimi's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Baqsimi should be used.

This summary of the RMP for Baqsimi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR)].

Important new concerns or changes to the current ones will be included in updates of Baqsimi's RMP.

I The Medicine and What It is Used for

Baqsimi is authorised for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 1 years and over with diabetes mellitus (see SmPC for the full indication). It contains glucagon as the active substance, and it is given by nasal dosing device.

Further information about the evaluation of Baqsimi's benefits can be found in Baqsimi's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

Link to the EPAR summary landing page.

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Baqsimi, together with measures to minimise risks about Baqsimi, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- important advice on the medicine's packaging.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Baqsimi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Baqsimi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Inappropriate use of the device leading to loss of drug benefit
Missing information	None

II.B Summary of Important Risks

Important potential risk: Inappropriate use of the device leading to loss of drug benefit	
Evidence for linking the risk to the medicine	In an emergency setting, the first-time user who is not familiar with the device or its instructions for use may fail to administer the medication correctly to the patient.
Risk factors and risk groups	Risk groups for inappropriate use of the device are likely to be first-time users who are unfamiliar with the device and the instructions for use.
Risk minimisation measures	Routine risk minimisation measures: Instructions for proper use of glucagon—SmPC Sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal and other handling), PL Section 3 (How Baqsimi is to be given), IFU (Important points to know and preparing the dose), device carton (Do not press the plunger prior to insertion as you will lose the dose), and tube container (Do not press plunger before insertion).. Instructions for patients to discuss the proper use of glucagon with family and friends before it is needed—PL Section 2 (What you need to know before you receive Baqsimi) and IFU (Initial statement). Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How Baqsimi is to be given), and IFU (After giving the dose). Additional risk minimisation measures: • Administration leaflet • Online instructional video • Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device

Abbreviations: IFU = Instructions for Use; PL = package leaflet; SmPC = Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of

Baqsimi.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for Baqsimi.

Part VII: Annexes

Table of Contents

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
Specific Adverse Event Reaction Baqsimi Follow-up Questionnaire (Reference AMP [redacted])	Lack of drug benefit

Specific Adverse Event Reaction Baqsimi Follow-up Questionnaire (Reference AMP [redacted])

Reported Events:

Date: _____ **Lilly Case #:**_____

Information Provided By: _____ **Signature / Initials:** _____ **Fax:**_____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ____Female _____Male _____Unknown **Race:** _____Caucasian _____Asian _____Black _____Other

Weight: _____ lb **Height:** _____ in

Parent/Guardian Contact Information (if patient is a minor): Name: _____ Phone Number: _____

Reported Drug: Baqsimi ® (nasal glucagon) **Lot/Control Number (if available):** _____

Reason for Administration: _____ **Date of Administration:** _____

Was nasal glucagon administered in the nose? ___Yes ____No If no, please explain_____

Who administered nasal glucagon? ____Self ____Healthcare Professional _____ Other (please explain): _____

Was nasal glucagon administered by a trained user? _____Yes _____No

Did the administrator review the PIL/IFU prior to administration? _____Yes _____No

Who trained the administrator (i.e., HCP, patient, self-directed): _____

Were educational materials used as part of the training? _____Yes _____No

If so, what materials were used?
Instructional video _____
Demonstration kit including trainer device and administration leaflet _____

When was the shrink wrap removed from the product? ___ Just prior to use ___ at an earlier time

If removed at an earlier time, please specify: _____

Did the user attempt to prime the device prior to use? _____Yes _____No

Was the plunger completely depressed so it was flush with the base? _____Yes _____No

Was the green line on the plunger visible after use? _____Yes _____No

What was the blood sugar level right before nasal glucagon was administered? _____ **mg/dl**

What was the blood sugar level after nasal glucagon was administered? _____ **mg/dl**

How long after the administration of nasal glucagon was the blood sugar level checked? _____ Minutes _____Hours

Hospitalized for this event? _____Yes _____No

Relevant Diabetic History: _____

Please list Concomitant Medications/Substances (include prescription, over the counter medications, and herbal medications): _____

Was this event related to nasal glucagon? _____Yes _____No _____Unknown

What was the Event Outcome _____Recovered _____Not Recovered _____Worsened _____Unknown

***Please provide rationale for relatedness assessment: _____**

Contact information of person who administered nasal glucagon:

Name:_____ Phone Number: _____
Address:_____
City:_____ State:_____ Zip Code:_____

Physician Contact Information:

Physician:_____ Phone Number:_____
Address:_____
City:_____ State:_____ Zip_____

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Draft key messages of the additional risk minimisation measures

The below items will contain the key points regarding the correct handling and administration of Baqsimi, especially the importance of

- not priming the device in advance
- not removing the shrink wrapping or removing the tube in advance of administering Baqsimi
- ensuring that the patient understands that while the trainer device used during demonstration can be reset/reused, each Baqsimi device can only be used once
- referring to the PL/IFU for more detailed information regarding administration and handling of Baqsimi
- referring to the online instructional video for a demonstration regarding correct handling and administration of Baqsimi
- ensuring that the trainer device is not inserted into a patient's nostril when demonstrating (that is, to observe prudent hygiene measures) (applicable to the trainer device only), and
- not routinely carrying the training device and Baqsimi together (applicable to the trainer device only).

Patients/caregivers Educational Materials:

- Administration leaflet
- Online Instructional video
- Demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device

Administration leaflet

Patients will receive the administration leaflet from the HCPs who are expected to prescribe and/or supply Baqsimi upon initial Baqsimi prescription. The leaflet will also include a patient alert card. Healthcare professionals who are expected to prescribe and/or supply Baqsimi will use this leaflet to train patients and/or caregivers on how to use Baqsimi and give the leaflet to the patient after the training. Patients can use the leaflet to teach those around them how to correctly handle and administer Baqsimi. The leaflet will also contain a URL and, where required, a password to a website where patients can access the instructional video online (see below).

Online instructional video

To further reinforce the correct Baqsimi handling and administration, an online instructional video will demonstrate the step-by-step instructions on the appropriate use of Baqsimi.

Demonstration kit with trainer device and administration leaflet unique to the trainer device

The demonstration kit consists of a trainer device with an administration leaflet, which is a non-drug containing device, and a box with instructions on how to use Baqsimi. It will be used by HCPs who are expected to prescribe and/or supply Baqsimi in order to educate patients and/or caregivers. In addition to instructions for correct handling and administration, the demonstration

kit contains key points that HCPs who are expected to prescribe and/or supply Baqsimi should emphasize when training patients and/or caregivers on Baqsimi.

Annex 7 - Other Supporting Data (including referenced material)

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