EU Risk Management Plan for EURneffy 1 mg and 2 mg (adrenaline nasal spray)

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 01 November 2024

Date of final sign off: 15 April 2026

Rationale for submitting an updated RMP: Final version update to 3.0 with text in **Table Part I.1 – Product Overview** updated to proposed text and initiation of log in **Annex 8 Summary of changes to the risk management plan over time**.

Summary of significant changes in this RMP:

- Final version updated to 3.0
- Table Part I.1 – Product Overview updated to proposed text approved in version 2.3
- List of all significant changes to the Risk Management Plan over time included in Annex 8

QPPV name: [redacted]

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Adrenaline.
Pharmacotherapeutic group(s) (ATC Code)	Cardiac stimulants excluding cardiac glycosides, adrenergic, and dopaminergic agents. ATC code: C01CA24.
Marketing Authorisation Applicant	ALK-Abelló A/S
Medicinal products to which this RMP refers	2.
Invented name(s) in the European Economic Area (EEA)	EURneffy 2 mg (adrenaline nasal spray). EURneffy 1 mg (adrenaline nasal spray).
Marketing authorisation procedure	Centralised.
Brief description of the product	Pharmacotherapeutic group: Cardiac stimulants excluding cardiac glycosides, adrenergic, and dopaminergic agents. *Adrenaline* Mechanism of action Adrenaline is a non-selective agonist of all adrenergic receptors, including alpha- and beta-adrenergic receptors. Binding to these receptors triggers a number of changes. Through its action on alpha-adrenergic receptors, adrenaline lessens the vasodilation and the increased vascular permeability that occur during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, adrenaline causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing and dyspnoea that may occur during anaphylaxis. Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

Hyperlink to the Product Information	The product information is included in Module 1.3.1 of the eCTD sequence.
Indication(s) in the EEA	EURneffy (adrenaline nasal spray) is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis. Treatment is indicated for adults and children aged 4 years and over with a body weight of 15 kg or more.
Dosage in the EEA	EURneffy (adrenaline nasal spray) should be administered at the first sign of an allergic reaction. The recommended dose for patients aged 4 and over and weighing 30 kg or more is a single intranasal administration of 2.0 mg adrenaline. The recommended dose for patients aged 4 and over and weighing 15 - <30 kg is a single intranasal administration of 1.0 mg adrenaline. In the absence of clinical improvement after 10 minutes, or if deterioration occurs or symptoms reappear after the initial treatment, a second dose may be administered. If symptoms continue to progress after use of this medicinal product, the patient should be advised to seek emergency help immediately. *Paediatric population 4 years or above:* EURneffy 2 mg may be used in persons 30 kg body weight. EURneffy 1 mg may be used in persons 15 - <30 kg body weight. The safety and efficacy of EURneffy in children below 4 years of age and weighing less than 15 kg has not been established.
Pharmaceutical form(s) and strengths	Nasal spray, solution in single-dose container.

Is/will the product be subject to additional monitoring in the EU?	Yes.

Part II: Safety Specification

Part II: Module SI - Epidemiology of The Indication(s) And Target Population(s)

Anaphylaxis is a life-threatening, systemic hypersensitivity reaction (Joint Task Force on Practice Parameters, 2005). It is the most severe form of allergic reaction and is almost always unexpected (Tang, 2009). Delay in clinical diagnosis and treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters, 2005). There are an estimated 20 million people in the United States with severe allergic reactions and at risk of anaphylaxis. The incidence of actual anaphylaxis in the United States is 49.8 cases per 100,000 person-years (Tang, 2009), translating to approximately 150,000 events a year. Lifetime prevalence of an anaphylaxis event is up to 2%, with a mortality rate of approximately 1% (Kemp, 2007, Tang, 2009, Arnold, 2011). The prevalence of anaphylactic reactions in different parts of Europe and different subpopulations has been extensively described in the literature. The prevalence is typically described as events per 100,000 persons per year with a relatively wide variance observed.

By far the highest prevalence is described by a report from 2012 in Spain, in the subpopulation of children aged 0-4 years. The prevalence reported for this subgroup is 313.58/100,000 persons/year (Tejedor Alonso *et al*., 2012). As this group only represents a fraction of the overall population, this figure should not be regarded as a realistic estimate of the actual number of cases in any country. The highest reported prevalence is 40.4 events/100.000 persons per year for adults in Denmark (Ruiz Oropeza *et al*., 2017).

Adrenaline is considered as the first-line drug of choice for allergic emergencies. Adrenaline also effectively reverses the symptoms of rhinitis, urticaria, bronchospasm, and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels, and other tissues. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of severe allergy events leading to anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in the published literature.

Commercially available adrenaline autoinjectors are the current out-of-hospital practice standard of care and in some situations is prescribed to all patients who have experienced anaphylactic reactions or are at risk of anaphylaxis. When properly used, these devices can allow for early administration of adrenaline to stop or reduce the intensity of the systemic allergic reaction before refractory anaphylaxis develops.

Early injection of adrenaline in anaphylaxis, defined as injection when severe allergic reaction starts, but before leading to anaphylaxis or Emergency Department (ED) arrival, can significantly reduce the likelihood of hospital admission, as compared with initial injection after ED arrival. Delayed injection of adrenaline has been reported in other anaphylaxis-related fatalities in which only 23% of the 92 individuals received adrenaline before anaphylactic shock and cardiac arrest. However, it has been well documented that the sooner administration of adrenaline can occur the less severe the systemic allergic reaction may become and less likely it will develop into an anaphylaxis event, or at least less severe (Campbell, 2014, Casale, 2022).

Although adrenaline injection has an excellent post-approval safety profile and is highly effective in the management of anaphylaxis, auto-injectors are considered inconvenient and cumbersome, particularly for paediatric patients, because use of the product requires administration intramuscularly or subcutaneously by patients themselves or by a caregiver in an emergency setting. The difficulty for patients to even carry the auto-injectors is a documented concern by medical professionals as the devices are not always available when needed in an emergency situation. Furthermore, apprehension to use an auto-injector due to the pain,

cost, and reluctance to use the device in a public setting often leads to delays in the treatment of severe allergic reactions in emergency situations. Delayed treatment is known to lead to more severe events and more frequent fatalities. Thus, the use of adrenaline auto-injection is one of the common reasons for the lack of use of adrenaline in emergency situations leading to poor treatment outcomes (Simons, 2010, Campbell, 2014, Casale, 2022).

Reported rates of patients with anaphylactic reactions receiving adrenaline in medical practice range from 27% to 44%, while only 4 to 10% receive more than one dose (Alvarez-Perea et al., 2017, Grabenhenrich et al., 2018, Grabenhenrich et al., 2019).

Part II: Module SII - Non-clinical Part of The Safety Specification

Adrenaline occurs naturally in the human body as well as in other vertebrates and even some invertebrate species. The use of adrenaline in the indication of serious allergic and anaphylactic reactions is well-documented in the published literature.

Given the clinical history of adrenaline injection, the pharmacology, pharmacokinetics, toxicology, and general safety are well understood. Since it was first approved for marketing almost 30 years ago, a large amount of the relevant data on the safety and efficacy of adrenaline is derived from prior clinical use.

Primary Pharmacology

The primary pharmacology of adrenaline is established by investigators using an *in vitro* physiological sheep preparation infusion of adrenaline which was shown to significantly increased mean arterial pressure, cardiac output, and right atrial pressure with a little change in systemic vascular resistance or heart rate (Myburgh, 2006).

Adrenaline acts on both α- and β-adrenergic receptors. Through its action on α-adrenergic receptors, adrenaline lessens the vasodilation and the increased vascular permeability that occur during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on β-adrenergic receptors, adrenaline causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing and dyspnoea that may occur during anaphylaxis. Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

Secondary Pharmacology

Secondary pharmacological effects are described in published studies which have shown that adrenaline produces a dose-dependent and potent increase in all cardiovascular parameters at 0.1 to 2.0 mg/kg. Mean QT/QTc intervals were not influenced. Counting of extra-systoles showed a dose-dependent increase during intravenous drug administration starting at a threshold dose of 0.1 mg/kg (Hauser et al., 2005).

The rate of absorption of adrenaline after various routes of administration was studied in the rabbit (Gu *et al*., 1999). In a five-way crossover study, rabbits were administered adrenaline by inhalation, intramuscular or subcutaneous injection with intravenous adrenaline and intramuscular saline as the positive and negative controls, respectively. Concentrations of adrenaline were measured pre-dose and at interval to 180 minutes post-dose. Maximum plasma concentrations (C_{max}) of adrenaline were higher and occurred more rapidly (time to maximum plasma concentration, T_{max}), after intramuscular injection than after subcutaneous injection or inhalation.

[redacted]

[redacted]

[redacted]

[redacted]

Evaluation of Impact of Anaphylaxis on Adrenaline Absorption via Intranasal Administration

Two studies with EURneffy have been conducted in a dog model to evaluate whether anaphylaxis has an influence on the absorption of adrenaline when administered via the intranasal route. A pilot study was conducted to confirm the model was working properly in an anesthetized dog (Study Number 2021-4052). After confirmation in the pilot study that adrenaline levels can be properly measured in the anesthetize dog anaphylaxis model, a primary study was conducted in 14 dogs (Study Number 2021-4072). This included a sequential administration of EURneffy with and without anaphylaxis. The primary objective of this part of the study was to measure pharmacokinetics and to determine if anaphylaxis altered the absorption of adrenaline by the intranasal route of administration.

The results of the GLP study 2021-4072 where animals were dosed in a normal state and then when experiencing anaphylaxis including severe hypotension and facial oedema. The result was that an increase in absorption was observed in the anaphylaxis state presumably due to the oedema in the nasal mucosa. The significant hypotension experienced by the animals did not appear to impact the absorption of adrenalin from the EURneffy formulation when administered with the same nasal sprayer device as planned for commercial use. Thus, these experiments confirm that during an anaphylactic event the absorption of adrenalin intranasally from the EURneffy product, will not be delayed and that associated mucosal oedema may in fact accelerate absorption slightly over the someone in a normal condition not having anaphylaxis.

Cytochrome P450 Reaction Phenotyping of Adrenaline

An *in vitro* metabolism study showed that adrenaline is rapidly metabolized by cytochrome P450 isoforms CYP1A2, CYP2C9, and CYP3A4 (Study Number CYP0986-R23).

Toxicology

Adrenaline is secreted by the adrenal gland. Endogenous plasma concentrations in resting adults are normally less than 30 pg/mL but may increase markedly during stress with plasma adrenaline concentrations greater than 10,000 pg/mL (Wortsman, 2002). The acute exposure of adrenaline encountered with anaphylaxis treatment (300 to 500 pg/mL C_{max} per 0.3 mg IM dose), such as with intramuscular administration by autoinjectors, is considerably within the range of that experienced naturally with endogenous levels. Thus, assessment of adrenaline toxicity is not generally warranted, e.g., carcinogenicity, genotoxicity, developmental toxicity.

Single-dose Toxicity

A study was conducted to evaluate the toxicity and toxicokinetics of EURneffy 1 mg adrenaline nasal spray following intranasal administration in the rat model (Study Number 2555-002). A total of 5 groups consisting of 15 male and 15 female Sprague Dawley rats per group were on the main study. An additional 5 groups consisting of 3 to 6 animals/sex/group were designated as toxicokinetic animals. The EURneffy formulation included Intravail A3 (DDM) as part of the clinical formulation tested in human PK studies.

The results of this study demonstrated that a single intranasal instillation of EURneffy at a dose up to 0.8 mg was not associated with any mortality, clinical observations, changes in body weights or food consumption, ophthalmologic changes, changes in haematology or clinical chemistry parameters, macroscopic findings, or changes in organs weights. Based on these results, a No Observable Adverse Effect Level (NOAEL) of 0.8 mg was established in the rat. The LD_{50} data from published literature have demonstrated that adrenaline is toxic at higher dose levels (Lewis, 2004).

Repeat-dose Toxicity

Data from published reports suggest that multiple intravenous injections of adrenaline could induce glaucoma in rabbits (Grant, 1986).

Genotoxicity

Endogenous adrenaline is constantly present in the body and ranges from 30 pg/mL to 10,000 pg/mL under various forms of stress. Anticipated average exposures after administration of EURneffy 2 mg adrenaline nasal spray are between 300 pg/mL and 500 pg/mL, thus well within the endogenous exposure range. While there are published non-clinical studies with adrenaline dosed in various animal models, there is no anticipated risk of genotoxicity in humans at the doses being administered where levels are within the normal endogenous level of the body.

Carcinogenicity

While there are published non-clinical studies with adrenaline dosed in various animal models there is no anticipated risk of carcinogenicity in humans at the doses being administered where levels are within the normal endogenous level of the body. Carcinogenic studies conducted by the inhalation route were found negative (National Toxicology Program, 1990).

Developmental Toxicology

While there are published non-clinical studies with adrenaline dosed in various animal models there is no anticipated risk of developmental toxicology in humans at the doses being administered where levels are within the normal endogenous level of the body.

Adrenaline has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 15 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m^2 basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis).

Haemorrhages, oedema and necrosis of distal extremities were observed when 5 to 50 µg of adrenaline was injected directly into rabbit foetuses at 18 to 22 days of gestational age (Shepard, 1986).

Adrenaline is shown to have potential teratogenic activity as observed by the foetuses with gastroschisis (Auletta, 1971), and abnormally absent aortic arches related to dysrhythmogenesis (Rajala *et al*., 1988) were

also reported and has been shown to affect the ovum transport and the motility of the rabbit oviduct (Longley et al., 1968) and impair implantation in rats (Crist and Hulka, 1970).

Local Tolerance

A study was conducted to evaluate the ocular tolerability of EURneffy 1 mg adrenaline nasal spray following single topical administrations in naïve New Zealand white rabbits (Study Number 2555-004). This study was conducted to evaluate the effects of ARS-1 if accidentally sprayed into the eyes. EURneffy was well tolerated based on indirect ophthalmoscopy, slit-lamp biomicroscopy and Modified Hackett-McDonald Scoring. There were no abnormal clinical observations or effects on body weights and no macroscopic lesions were observed at necropsy. Given the lack of any signs of toxicity due to accidental exposure into the eye, and that epinephrine is indicated for use in the eyes using drops and via injection, no further studies were considered warranted.

Other Toxicity Studies

Adrenaline caused significant decrease in cardiac index, ejection fraction and pH and a concomitant increase in systemic vascular resistance and serum creatinine when compared with norepinephrine and vasopressin (Minneci *et al*., 2004) and is also associated with metabolic effects, decreased mesenteric, coronary, and renal conductance in a sheep model of septic shock (Di Giantomasso *et al*., 2005).

There were no new safety findings of relevance to human usage that have not already identified from any of the non-clinical studies conducted by the Applicant or identified from the published scientific literature.

Part II: Module SIII - Clinical Trial Exposure

Adrenaline is the adrenergic drug of choice for the emergency treatment of acute hypersensitivity (anaphylactoid reactions to drugs, animal serums, insect stings, and other allergens): for symptomatic relief of serum sickness, urticaria, angioneurotic oedema and respiratory distress due to bronchospasm. Controlled efficacy studies have not been conducted with either injection forms of adrenaline or EURneffy (2 mg or 1 mg) adrenaline nasal spray (as controlled studies in anaphylaxis are not considered ethical), however, the efficacy of adrenaline is well documented by extensive clinical use.

To assess the response to EURneffy 2 mg adrenaline nasal spray (code-named ARS-1 in trials), an assessment of pharmacodynamic (PD) responses to EURneffy 2 mg adrenaline nasal spray compared to EpiPen, IM and SC adrenaline injections was conducted (see Tables SIII.1-4 below). The results from 3 primary clinical trials (EPI 15, EPI 16 and EPI 17) demonstrate that EURneffy 2 mg adrenaline nasal spray has similar PD responses on blood pressure and heart rate in adults as would be expected in the treatment of anaphylaxis (Table SIII.1). These biomarkers are predictors of efficacy and given that efficacy studies in anaphylaxis are considered unethical, the combined PK and PD comparisons performed, demonstrate that the absorption and effect of adrenaline from EURneffy 2 mg adrenaline nasal spray dosing by intranasal administration should be at least as effective as EpiPen and may be better than IM/SC injection. An additional clinical study evaluates repeat dosing of EURneffy under nasal allergen challenge conditions (study EPI 18). The results show that the EURneffy PK and PD profile is greater than or similar to intramuscular injection. In particular, repeat dosing in the same nostril was greater in exposure than dosing once in each nostril and greater than injection on both PK exposures and PD response at all time points.

In addition to the 3 primary clinical trials in adults with EURneffy 2 mg, data from the EPI 10 clinical trial including 21 children 15 - <30 kg who received EURneffy 1 mg and 21 children ≥30 kg who received EURneffy 2 mg confirms that EURneffy 2 mg adrenaline nasal spray has similar PK and PD responses on blood pressure and heart rate in paediatric subjects ≥30kg is similar or slightly higher than in adults (Table SIII.1). Given there is no significant effect of weight on exposure from either IM or nasally administered epinephrine these results also support use of the 2 mg EURneffy product in both adults and paediatric subjects ≥30 kg. In addition to these primary studies conducted with the EURneffy 2 mg formulation, a number of supportive trials on a 1 mg dose of EURneffy have been conducted in adults, which supports the use of 1 mg EURneffy in paediatric patients from 15 kg to <30 kg body weight. Supportive PK, PD and safety data are included in the Marketing Authorisation Application from 6 clinical trials (EPI 03, EPI 04, EPI 07, EPI 11b, EPI 12 and JP01) conducted with EURneffy 1 mg (Table SIII.2). The PD response in these studies also supports that even the 1 mg dose provides very similar PD responses as compared to currently approved injection products.

Other studies conducted are either small pilot studies (EPI 06 and EPI 11) or are compromised by study conduct issues including during the COVID pandemic (EPI 09 and EPI 13) and not presented as primary for approval.

None of the studies conducted by the Applicant with EURneffy 2 mg or EURneffy 1 mg doses detected any new safety concerns above and beyond those already established for adrenaline administered by other routes for the same indication. The fact that EURneffy does not include a needle and is not by the injection route of administration means there are inherent safety benefits of the intranasal route given that many of the most significant side effects of epinephrine autoinjectors is directly related to the needle and device. This includes the potential to injection into a blood vessel (i.e., bolus IV injection that can lead to serious

cardiovascular events including cerebral haemorrhage), lacerations, bone injections, as well as self-injection into an extremity by the patient or a caregiver resulting in the need for emergency treatment to prevent necrosis.

Table SIII.1: EURneffy 2 mg and 1 mg Studies for MAA

Trial	Trial Description	Trial Size / Status
EPI 15 *[Pivotal study for PD and PK outcomes]*	A Two-Part, Six-Period, Six-Treatment, Crossover Study of the Pharmacokinetics of Epinephrine After Single and Repeat Administration of Intranasal ARS-1 or Epinephrine Injection to Healthy Volunteers.	n = 59 subjects. Completed.
EPI 16 *[Pivotal study for PD and PK outcomes]*	A Four-Treatment, Partially Randomized, Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis (EPI 16).	n = 36 subjects. Completed.
EPI 17 *[Pivotal study for PD and PK outcomes]*	A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self-Administration of Epinephrine with Intranasal ARS-1 as compared to IM injection in Subjects with Type I Allergies.	n = 42 subjects. Completed.
EPI 10 *[Pivotal study for PD and PK outcomes for pediatrics 15kg+]*	A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Pediatric Subjects with Systemic Allergies (interim analysis).	n = 80 subjects. Subjects 15 – <30 kg 0.65 mg (n = 12) 1 mg (n = 21) Subjects ≥ 30 kg 1 mg (n = 26 2 mg (n = 21) Completed.
EPI 18 *[Pivotal study for PD and PK outcomes after repeat dosing]*	A Five-Treatment, Five-Period, Randomized, Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Repeat Administration of neffy and Intramuscular Epinephrine Injection in Type I Allergy Patients with Seasonal Rhinitis	N= 43 subjects. Completed.

Table SIII.2: Supportive EURneffy 1.0 mg Studies

Trial	Trial Description	Trial Size / Status
EPI 03 *[Supportive study for PD and PK outcomes]*	A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of ARS-1 and IM Epinephrine to Healthy Volunteers.	n = 70 subjects. Completed.
EPI 04 *[Evaluate effect of Rhinitis on absorption]*	A Five-Treatment, Partially-Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis.	n = 36 subjects. Completed.

Trial	Trial Description	Trial Size / Status
EPI 07 *[Supportive study for PD and PK outcomes]*	A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 or EpiPen to Healthy Volunteers.	n = 36 subjects. Completed.
EPI JP01 *[Evaluate PD and PK [redacted] Assess effect of Rhinitis]*	A Five-Treatment, Partially-Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1, 0.3 mg and 0.5 mg IM injection or EpiPen [redacted] with Allergic Rhinitis.	n = 36 subjects. Completed.
EPI 11B *[Supportive study for BA and PK]*	A Five-Period, Five-Treatment, Randomized, Crossover Study in Two Groups to Evaluate the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 to Healthy Volunteers.	N = 26 subjects. Completed.
EPI 12 *[Supportive study for PD and PK outcomes]*	A Four-Period, Four-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self-Administration of Epinephrine with Intranasal ARS-1, EpiPen, and Symjepi in Subjects with Type I Systemic Allergies.	n = 42 subjects. Completed.
EPI 14 *[Supportive study for PD and PK outcomes]*	A Single-dose, Two-period Study to assess PK after IN Administration of ARS-1 in Subjects with Normal Nasal Conditions and with a URTI.	N = 21 subjects Completed
EPI JP02 *[Supportive study for PD and PK outcomes]*	Phase 1, Two-period, Two-treatment, Randomized, Crossover Study of the Comparative Bioavailability of Adrenaline after Administration ARS-1 2.0 mg or Adrenaline 0.3 mg IM [redacted]	N = 13 subjects Completed
EPI JP03 *[Supportive study evaluating efficacy following oral food challenge in pediatric patients]*	A Phase 3, Single-period, Single-dose Study Evaluating Efficacy and Safety of Adrenaline of ARS-1 in Patients with Food Allergies.	N = 15 subjects Completed

Table SIII.3 details the age-groups and genders of subjects in completed studies with the commercially manufactured EURneffy 2 mg product (EPI 10, EPI 14, EPI 15, EPI 16, EPI 17, EPI 18, EPI JP02, and EPI JP03) [redacted] and in supportive studies with EURneffy 1 mg (EPI 02, EPI 03, EPI 04, EPI 07, EPI 10, EPI 11B, EPI 12, EPI JP01, and EPI JP03).

Table SIII.4 details number of doses at a given dose studied in the clinical trial program.

Table SIII.3: Age Group and Gender

Age group	Patients	
	Male	Female
EURneffy 2 mg (EPI 10, EPI 14, EPI 15, EPI 16, EPI 17, EPI 18, EPI JP02 and EPI JP03)		
Pre-term newborn infants	0	0
Term newborn infants (0 to 27 days)	0	0
Infants and toddlers (28 days to 23 months)	0	0
Children (2 to 11 years)	4	2
Adolescents (12 to 17 years)	14	10
Adults (18 to 64 years)	215	136
Elderly people (65+ years)	0	0
EURneffy 1 mg (EPI 03, EPI 04, EPI 07, EPI 10, EPI 11B, EPI 12, EPI JP01, and EPI JP03)		
Pre-term newborn infants	0	0
Term newborn infants (0 to 27 days)	0	0
Infants and toddlers (28 days to 23 months)	0	0
Children (2 to 11 years)	15	16
Adolescents (12 to 17 years)	14	8
Adults (18 to 64 years)	141	94
Elderly people (65+ years)	0	0
Other non-supportive or failed studies (EPI 06, EPI 09, EPI 11 and EPI 13)		
Pre-term newborn infants	0	0
Term newborn infants (0 to 27 days)	0	0
Infants and toddlers (28 days to 23 months)	0	0
Children (2 to 11 years)	0	0
Adolescents (12 to 17 years)	0	0
Adults (18 to 64 years)	67	54
Elderly people (65+ years)	0	0

Table SIII.4: Number of doses of each respective dose administered

Dosage of exposure	Doses given
EURneffy 2 mg[1]	481
EURneffy 1 mg (10 mg/mL)[2]	512
Other doses	
0.5 mg (5 mg/mL)	12
0.65 mg (6.5 mg/mL)	24
0.8 mg (8 mg/mL)	12
1.3 mg (13 mg/mL)	25
1.5 mg (15 mg/mL)	39
1.8 mg (18 mg/mL)	13
4 mg[3] (2 mg x2)	202
Total	**1,320**

[1] EURneffy 2 mg dose includes subjects that received a single 2 mg dose, subjects that received two 1 mg doses spaced 10 minutes apart, and subjects with and without Rhinitis.
[2] EURneffy 1 mg dose includes subjects with and without Rhinitis.
[3] EURneffy 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.

Results from the 6 primary studies that included EURneffy 2 mg for adults and children ≥ 30 kg (EPI 10, EPI 14, EPI 15, EPI 16, EPI 17, and EPI 18) demonstrate favourable pharmacokinetics, pharmacodynamics, and safety of EURneffy 2 mg adrenaline nasal spray compared to adrenaline injection and no new safety concerns were identified associated with either the new route of administration (intranasal) or the use of the novel excipient, Intravail A3 in the formulation. The results of EPI 10 also demonstrate favourable pharmacokinetics, pharmacodynamics, and safety of EURneffy 1 mg for pediatric patients 15 - < 30 kg). The results of study EPI 18 show that the EURneffy PK and PD profile is greater than or similar to intramuscular injection. In particular, repeat dosing in the same nostril was greater in exposure than dosing once in each nostril and greater than injection on both PK exposures and PD response at all time points.

In addition, results from the 8 supportive EURneffy 2 mg and 1 mg studies (EPI 02, EPI 03, EPI 04, EPI 07, EPI 11B, EPI 12, EPI JP01, EPI JP02, and EPI JP03) also demonstrate favourable PK, PD, and safety of the EURneffy up to 2 mg adrenaline nasal spray.

Finally, other non-supportive trials (EPI 06, EPI 09, EPI 11 and EPI 13) confirm the safety of various doses of EURneffy up to 2 mg.

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Due to the nature of the condition (emergency treatment of anaphylaxis), it is not considered ethical to conduct clinical trials in actual patients and as such the studies were predominantly conducted in healthy volunteers, as well as in subjects with history of allergic conditions (Primary studies with EURneffy 2 mg EPI 14, EPI 15, EPI 16, EPI 17, EPI 18, and EPI 10; and EURneffy 1 mg EPI 04, EPI 12, EPI JP01, and EPI 10).

The main aim of the clinical program was conducted to establish the PK and PD parameters of EURneffy 1 mg and 2 mg adrenaline nasal spray. These studies were conducted in adult and paediatric subjects (healthy volunteers or allergy patients) 15 - <30 kg (EURneffy 1 mg) and ≥30 kg (EURneffy 2 mg) regardless of age, which is the standard for dosing of injection products.

Due to the nature of the studies, the objective behind the clinical program and given the fact that adrenaline and its use is well documented along with its use in different sub-populations, none of the important exclusion criteria in the pivotal studies are considered to constitute missing information for the purposes of this risk management plan.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Due to the nature of the clinical development programme, it 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.

However, given the nature of the drug and the intended indication, none of these assumptions are considered to be of concern due to the fact that the safety profile of adrenaline is very well documented, the intended use is for acute emergency treatment and the intended route of administration is not likely to give rise to any new safety concerns not already known for adrenaline.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Given the nature of the development program and its intended aim, no special populations were included in any of the clinical trials conducted; given that the intended product labelling mirrors that of products already approved for the same indication it is not considered that the development program constitutes a limitation in the ability to identify safety concerns in special populations as the program by definition was not designed or intended to be able to do so.

Table SIV.2: 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 program.
Breastfeeding women	
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 program.
Subpopulations carrying relevant genetic polymorphisms.	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for The Safety Specification

Potential for misuse for illegal purposes

EURneffy 2 mg and EURneffy 1 mg are prescription-only medications, which limits the potential for abuse. There is no addiction potential with adrenaline.

Part II: Module SVII - Identified and Potential Risks

The safety concerns are based on the risks published for adrenaline on the CMDh website, as well as information gathered via the clinical programme for EURneffy 2 mg and EURneffy 1 mg. As adrenaline is often administered by the intramuscular route via injection, some further potential risks relating to the administration of adrenaline via a nasal spray form have been identified and are discussed below.

SVII.1 Identification of safety concerns in the initial RMP submission

The risks discussed below fall into either the important identified risk or important potential risk category. Identified risk refers to a risk for which there is an undesirable clinical outcome and for which there is sufficient evidence to suggest that it is caused by the medicinal product. Potential risk refers to a risk for which there is an undesirable clinical outcome, and for which there is sufficient scientific evidence to suggest that the possibly of a causal relationship with the medicinal product, but for which there is insufficient evidence to conclude a definite causal relationship. The list of risks not considered important for inclusion are also discussed.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Not applicable.

Adverse reactions with clinical consequences, even serious, but occurring in low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse event reporting, and for which the risk minimisation messages in 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):

- Use in patients with high intraocular pressure
- Use in patients with severe renal impairment
- Use in patients with prostatic adenoma, leading to residual urine, hypercalcaemia, and hypokalaemia
- Use in patients with Parkinson’s disease
- Use with drugs that may sensitise the heart to arrhythmias
- Use in patients with hyperthyroidism, cardiovascular disease, hypertension
- Use in patients with diabetes
- Use in elderly

- Use in pregnancy

These risks are included in the Summary of Product Characteristics (SmPC) for EURneffy 2 mg and EURneffy 1 mg within the 'Special warnings and precautions for use' section. Healthcare professionals prescribing EURneffy 2 mg will be aware of these warnings and should be satisfied that the benefit of using EURneffy 2 mg outweighs any potential risks.

Known risks that do not impact the risk-benefit profile:

Potential for abuse

The potential for abuse of EURneffy 2 mg and EURneffy 1 mg is reduced by the lack of any observable euphoric effect. EURneffy 2 mg is a prescription-only medication, which limits the potential for abuse. There is no addiction potential with adrenaline.

Potential for off label use

Adrenaline is often used for other indications than anaphylactic reaction, particularly within a hospital setting. The potential risk of off label use of EURneffy 2 mg and EURneffy 1 mg in other indications is reduced by the formulation, as injection formulations are far more likely to be used in a hospital setting.

Potential for overdose

The potential risk of overdose with EURneffy 2 mg and EURneffy 1 mg is reduced by the single-dose formulation, with a limited dose. As EURneffy 2 mg and EURneffy 1 mg are intranasal formulations, the potential risk of overdose associated with the use of an intramuscular preparation accidentally being administered intravenously is mitigated.

Adrenaline in the central nervous system (CNS)

Intranasal administration allows for the bypass of first pass metabolism and the blood-brain barrier via the olfactory and trigeminal nerves (Crowe, 2018). The blood-brain barrier is impermeable to adrenaline and therefore adrenaline would not usually be expected to be present within the central nervous system (Chen, 2012). In the case of administration of EURneffy 2 mg and EURneffy 1 mg adrenaline could reach the central nervous system, including the brain.

Data from studies has demonstrated no CNS effects following intranasal adrenaline administration. The restricted access of epinephrine to the brain removes the potential for the therapeutic effect of adrenaline in the CNS.

Serious allergic reaction to sodium metabisulfite

EURneffy contains a small concentration of sodium metabisulphite as an excipient. Patients with a sensitivity or allergy to sulphites may therefore experience allergic reactions. In patients where the sensitivity is considered mild, the benefit of using EURneffy in the indication of an anaphylactic reaction would likely outweigh the potential risk, and treatment should not be delayed.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks

No important identified risk was selected.

Important potential risks

Medication error

Risk-benefit impact:

As the indication of anaphylactic reaction is potentially life-threatening, failure of the device to work as intended represents a risk. If administered promptly following an anaphylactic reaction, adrenaline is highly effective and can be lifesaving. As incidence of severe allergies increases worldwide, it becomes more important that patients and caregivers are able to effectively treat those that experience anaphylactic reactions promptly.

Symptoms of severe anaphylaxis can include bronchoconstriction, respiratory arrest, hypotension and circulatory collapse. Administration of adrenaline during a severe allergic reaction result in increase in vasoconstriction, bronchodilation, increased output of the heart due to vasodilation of coronary arteries, increased heart rate and contractility of cardiac muscle. This will therefore improve breathing and increase systolic blood pressure, treating the symptoms of a severe allergic reaction to prevent progression to anaphylaxis. Adrenaline can also treat anaphylaxis if the reaction progresses to that severe situation (Ring, 2018).

Intramuscular injections of adrenaline via an auto-injector have been used as a successful treatment for anaphylactic reactions for many years. EURneffy 2 mg and EURneffy 1 mg are designed to be used by lay people, to allow for easy, rapid self-administration in an allergy emergency in order to treat the symptoms of a serious allergic reaction before it can progress to anaphylaxis. It is beneficial that EURneffy 2 mg and EURneffy1 mg are delivered as a single dose, as it eliminates the risk of delayed or inaccurate dosing (Sicherer, 2017).

The use of autoinjectors is more complex and difficult than EURneffy 2 mg and EURneffy1 mg. Human factor studies with the EURneffy device demonstrate that the updated Instructions for Use and Quick Reference Guide were well understood by subjects and no unanticipated dosing errors were reported. EURneffy can be easily used by patients, caregivers, adolescents, and passerby persons based on the Instructions For Use as included in the Summary of Product Characteristics and Patient Information Leaflet.

Products that patients can administer to themselves during an anaphylactic reaction are therefore of benefit, in order to reduce the likelihood of the reaction becoming serious, requiring hospitalisation or being fatal. The benefit of being able to easily carry and rapidly administer adrenaline using a small nasal sprayer device will outweigh the risk of administering the product incorrectly.

Lack of drug effect in the indication of an anaphylactic reaction could be potentially fatal. It is therefore of crucial importance that the product has the intended effect and is efficacious. Use of expired products may result in a sub-therapeutic response. Patients and caregivers should ensure that all devices are within their

expiry date and that new nasal spray devices are requested when the expiry date is nearing, to ensure that if the product is required in an emergency situation, that it is has not already expired.

Missing information

No missing information identified.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable for an initial application.

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:

No important identified risk was selected.

Important potential risk: Medication error

Potential mechanisms:

Patients or caregivers may attempt to operate the device incorrectly by depressing the plunger too soon. This may result in only a partial dose of EURneffy 2 mg or EURneffy 1 mg being administered, leading to a potential lack of efficacy. A single dose of EURneffy 2 mg or EURneffy 1 mg may be inadequate for some patients to relieve the symptoms of a severe allergic reaction.

Given the indication, a lack of drug effect would likely constitute a life-threatening serious adverse event. There is a risk that out-of-date medication could be used, particularly if a patient is not frequently seeing their healthcare professional. Out of date medication may be less efficacious, and given the seriousness of the indication, it is essential that the product works as intended in a potentially life-threatening situation.

Evidence source(s) and strength of evidence:

As the indication of an anaphylactic reaction is potentially life-threatening, it is essential that the medicine works as intended. A lack of efficacy could have life-threatening implications. Delaying treatment with adrenaline can also result in a lack of efficacy and is associated with fatal anaphylaxis (Campbell, 2014, Casale, 2022). Operating the device incorrectly causing only a partial dose of EURneffy 2 mg or EURneffy 1 mg to be administered is an important potential risk because failure to activate EURneffy 2 mg or EURneffy 1 mg during a severe allergic may reduce the effectiveness of the medication and require a second dose. It is also important to understand that a second dose of EURneffy 2 mg or EURneffy1 mg may be needed for more severe cases of allergic reactions, or if the use of EURneffy 2 mg or EURneffy1 mg was delayed or mistake in administration occurs. Lack of drug effect during a severe anaphylactic reaction may allow the symptoms to worsen and in rare cases can be fatal if an additional dose is not given promptly.

Characterisation of the risk:

This risk was not observed in clinical studies involving EURneffy. Three Human Factors Validation studies were conducted. First one was with 90 persons (15 caregivers, 30 patients, 15 Passer byes; 15 medical professionals, 15 adolescents (12+) who were all untrained. Second one was a "bridging study" to qualify some changes in the dosing instructions (i.e. instructions for use and quick reference guide) with 60 persons (15 caregivers; 15 patients self-administration; 15 adolescents self-administration no training, 15 adolescents self-administration with training). Based on the two Human Factor Validation studies conducted, EURneffy can be easily used by patients, caregivers, adolescents, and passer-by persons based on the instructions for use and quick reference guide. The updated instructions for use were well understood by subjects and did not result in any unanticipated dosing errors. As a part of ongoing development from Study EPI 18, ARS has clinical data which demonstrates that when dosed twice (two doses 10 minutes apart) the use of the same nostril is not different from dosing twice into the opposite nostrils. A human factors study was conducted to validate acceptability of revised instruction for use, whereby users are instructed to administer the second dose (if one is required) to the same nostril. The study was conducted with 16 volunteers: four lay adults (age 20 -67) with a history of severe allergies; eight juveniles (age 10 – 17) with a history of severe allergies; four lay caregivers (age 33 -54). Based on the findings, it can be concluded that the updated labelling supports the intended administration steps and that the use of the same nostril is effective in preventing any potential use issues.

Routine pharmacovigilance will enable to establish the frequency of this risk in the post-marketing phase.

A specific follow-up questionnaire for use in the case of medication errors will be made available to collect further information and characterisation of this risk.

Risk factors and risk groups:

EURneffy 2 mg is indicated for use in persons aged 4 years or over with a body weight of ≥ 30 kg. EURneffy 1 mg is indicated for use in persons aged 4 years or over with a body weight of 15 - < 30 kg. If the patient is particularly young or elderly, he may experience issues administering the product correctly. If the patient is experiencing a severe reaction or anaphylaxis, the product could be administered by another person, who may be unaware of the proper administration technique. Risk factors also include use of expired medications, resulting in the dose not achieving the intended therapeutic effect.

Preventability:

In the event of a lack of efficacy it is stated in the reference safety information that EURneffy 2 mg and EURneffy 1 mg can be administered a second time after 5-15 minutes if the symptoms have not improved or have deteriorated following the first administration. It is also made clear that emergency medical help should be sought following a severe allergic reaction, or administration of EURneffy 2 mg or EURneffy 1 mg. Patients are advised to carry more than one EURneffy 2 mg or EURneffy 1 mg nasal spray at all times, in case of improper administration or insufficient pharmacological effect of a single dose.

Ensuring that the patient information leaflet contains clear guidance and illustrations detailing how to properly administer the product will greatly reduce the risk of EURneffy 2 mg or EURneffy 1 mg not working as intended in a critical situation. Physicians prescribing EURneffy 2 mg or EURneffy 1 mg should take appropriate steps to ensure that the patient understands how to use the nasal spray, as well as any other persons who may be in the position to administer EURneffy 2 mg or EURneffy 1 mg to a patient

experiencing a severe allergic reaction. The packaging of the product itself includes illustrations and instructions on how to properly administer the product.

Patients and caregivers ensuring that the product is within the expiry date before use is essential.

Impact on the risk-benefit balance of the product:

The impact of this risk is expected to be low, given the instructions for use provided in the Summary of Product Characteristics and Patient Information Leaflet. Patients are expected to use medications that are within the expiry date. This risk will be monitored via routine pharmacovigilance activities.

Public health impact:

Based on the available evidence, this safety concern is unlikely to affect a high number of individuals. The number of events expected to be related to this risk is low. The risk of medication errors, including mishandling of device for EURneffy 2 mg or EURneffy 1 mg can be managed appropriately through the instructions for use provided in the Summary of Product Characteristics and Patient Information Leaflet.

SVII.3.2. Presentation of the missing information

There is no missing information.

Part II: Module SVIII - Summary of The Safety Concerns

The summary of safety concerns presented below has been prepared based on clinical studies conducted on EURneffy and the publicly available information for adrenaline.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None.
Important potential risks	Medication error
Missing information	None.

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reporting and signal detection:

Given that careful monitoring of the use of the product in the post authorisation setting, is warranted, a specific follow-up questionnaire will be used in case of medication errors.

For details relevant to routine pharmacovigilance activities refer to PSMF.

III.2 Additional pharmacovigilance activities

No post-authorisation safety studies are imposed or are planned.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been imposed or are planned.

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

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Important potential risk: Medication error	*Routine risk communication:* SmPC section 4.2: Posology and method of administration. PL section 2: What you need to know before you use EURneffy. PL section 3: How to use EURneffy (Instructions for Use: to be included in the blister pack that contains the EURneffy device). *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the SmPC outlines the instructions for use for EURneffy 2 mg or EURneffy 1 mg adrenaline nasal spray. Section 4.2 of the SmPC advise that in the absence of clinical improvement after approximately 10 minutes, or if deterioration occurs or symptoms reappear after the initial treatment, a second dose should be administered in the same nostril. The patient should be advised to seek emergency medical assistance immediately to have close monitoring of the anaphylactic episode and in the event further treatment is required.

V.2. Additional risk minimisation measures

Additional risk minimization measures are as follows:

Training device.

Training devices will be made available to physicians such that the training device can then be provided to patients on request, via their physician.

Objectives:

Simulate the administration procedure before its actual use. This will reduce the risk of mishandling of the device and facilitate its correct use.

Rationale for the additional risk minimisation activity

This additional risk minimisation measure is needed to support patient training in the correct use of the device.

Target audience and planned distribution path

The target audiences are prescribing physicians and patients. The training devices will be distributed via a professional website, central fulfilment with direct shipments and company field representatives to physicians who make a request for a training device.

Evaluation of effectiveness of risk minimization measure

Records of distribution will be collected and maintained to measure information on availability of training device.

Training videos.

Training videos will be made available to physicians, patients and caregivers.

Objectives:

To allow prescribers, patients and caregivers to view how to properly administer the product. Self-administration by adult and adolescent, and caregiver administered videos will be made available to address the different scenarios for administration of the product.

Rationale for the additional risk minimisation activity

This additional risk minimisation measure is needed to support patient training in the correct use of the device.

Target audience and planned distribution path

The target audiences are prescribing physicians and patients. The training videos will be distributed via patient and professional websites.

Evaluation of effectiveness of risk minimization measure

Records of distribution/download will be collected and maintained to measure information on availability of training video.

Digital educational material

A patient education brochure will be provided to physicians upon request and on the EURneffy website in digital format.

Patient education brochure

Objectives:

To explain in detail how the product is to be used and the different steps for administration.

Rationale for the additional risk minimisation activity

This additional risk minimisation measure is needed to support how the product is to be used and the different steps for administration

Target audience and planned distribution path

The target audience is patients. The digital educational materials will be distributed via the EURneffy website in digital format and through physician offices supplied by company field representatives.

Evaluation of effectiveness of risk minimization measure

Records of distribution/download will be collected and maintained to measure information on availability of the patient education brochure.

Instructions for Use (IFU)

The IFU will be packaged within the blister containing the EURneffy device. Inclusion of the IFU within the EURneffy blister ensures that in the event that the Patient Information Leaflet is not retained with the EURneffy device, patients will have access to the key information on how to use the product.

Objectives:

To ensure that in the event that the Patient Information Leaflet is not retained with the EURneffy device, a patients will have access to the key information on how to use the product correctly.

Rationale for the additional risk minimisation activity

This additional risk minimisation measure is needed to support correct use of product and avoid medication errors.

Target audience and planned distribution path

The target audience is patients.

Evaluation of effectiveness of risk minimization measure

Manufacturing control and records will be collected and maintained to measure inclusion of the IFU within the device blister.

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
Important potential risk: Medication error	*Routine risk minimisation measures:* SmPC section 4.2: Posology and method of administration. PL section 2: What you need to know before you use EURneffy. PL section 3: How to use EURneffy (Instructions for Use: to be included in the blister pack that contains the EURneffy device). *Additional risk minimisation measures:* • training device • training videos • digital educational material • IFU within EURneffy device blister	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal:* Targeted questionnaire in case of medication errors. *Additional pharmacovigilance activities:* None

Part VI: Summary of The Risk Management Plan

This is a summary of the Risk Management Plan (RMP) for EURneffy 2 mg (adrenaline nasal spray). The RMP details important risks of EURneffy 2 mg and EURneffy 1 mg, how these risks can be minimised,

and how more information will be obtained about EURneffy 2 mg's risks and uncertainties (missing information).

EURneffy 2 mg and EURneffy 1 mg's summary of product characteristics and its package leaflet will give essential information to healthcare professionals and patients on how EURneffy 2 mg and EURneffy 1 mg should be used.

This summary of the RMP for EURneffy 2 mg and EURneffy 1 mg should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 EURneffy 2 mg and EURneffy 1 mg's RMP.

I. The medicine and what it is used for

EURneffy 2 mg and EURneffy 1 mg (adrenaline nasal spray) should be used for the emergency treatment of serious allergic reactions, including anaphylaxis.

EURneffy 2 mg and EURneffy 1 mg should be used by a person with a history or who may be at risk of an anaphylactic reaction. EURneffy 2 mg and EURneffy 1 mg are indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis.

Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhoea and abdominal cramps, involuntary voiding, wheezing, dyspnoea due to laryngeal spasm, pruritus, rashes, urticaria, or angioedema.

EURneffy 2 mg and EURneffy 1 mg should therefore always be carried by such persons in situations of potential risks.

Adrenaline is considered the first-line drug of choice for allergic emergencies. Adrenaline also effectively reverses the symptoms of rhinitis, urticaria, bronchospasm, and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels, and other tissues. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in the published literature.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of EURneffy 2 mg and EURneffy 1 mg (adrenaline nasal spray), together with measures to minimise such risks 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;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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

In the case of EURneffy 2 mg and EURneffy 1 mg, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of EURneffy 2 mg and EURneffy 1 mg (adrenaline nasal spray) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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 EURneffy. 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	Medication error.
Missing information	None.

II.B Summary of important risks

Important potential risk: Medication error	
Evidence linking the risk to the medicine	Operating the device incorrectly causing either no dose or a partial dose of EURneffy 2 mg or EURneffy 1 mg to be administered is an important potential risk because failure to use EURneffy 2 mg or EURneffy 1 mg properly during a severe allergic reaction can allow progression of the allergic reaction and in rare cases may be fatal. It is also important to understand that a second dose of EURneffy 2 mg or EURneffy 1 mg may be needed for more severe cases of allergic reactions, if the use of EURneffy 2 mg was delayed, or if EURneffy 2 mg or EURneffy 1 mg is not used properly. Lack of drug effect during a severe allergic reaction can allow progression of the disease and in rare cases may be fatal if an additional dose is not given promptly.
Risk factors and risk groups	EURneffy 2 mg is indicated for use in persons aged 4 years or over weighing ≥ 30 kg and EURneffy 1 mg is indicated for use in persons aged 4 years or over weighing 15 - <30 kg. If the patient is particularly young

	or elderly, he may experience issues administering the product correctly. If the patient is experiencing a severe reaction, or anaphylaxis, the product could be administered by another person, who may be unaware of the proper administration technique. Risk factors also include use of expired medications, resulting in the dose not achieving the intended therapeutic effect.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC section 4.2: Posology and method of administration. PL section 2: What you need to know before you use EURneffy. PL section 3: How to use EURneffy (Instructions for Use: to be included in the blister pack that contains the EURneffy device). *Routine pharmacovigilance activities beyond adverse reactions reporting and signal:* Targeted questionnaire in case of medication errors. *Additional risk minimisation measures:* Additional risk minimisation measures are as follows: • training device • training videos • digital educational material • IFU within EURneffy device blister

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of EURneffy 2 mg or EURneffy 1 mg (adrenaline nasal spray).

II.C.2 Other studies in post-authorisation development plan

There are no studies required for EURneffy 2 mg or EURneffy 1 mg (adrenaline nasal spray).

Part VII: Annexes

Table of Contents of Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only. Data will be forwarded electronically after MA approval.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific medication error follow-up form

Targeted follow-up questionnaire for medication errors:

Specific follow-up forms (for medication errors)

A. Patient Details:

Initials:		Age (at the time of medication error):	
Sex M / F		Weight (kg):	

Suspect Drug Details

Suspect drug:		Indication:	
Prescribed dose:	_____mg	Dosage form	Nasal spray
Dose actually used:	_____mg	Treatment date: _____ DD-MON-YYYY	Time between doses (if more than one dose administered _____minutes

B. Details of Medication Error

1. Describe Medication Error:

Please specify: _____

2. Classification of medication error:

☐ Error occurred during administration of medication

☐ Error was noticed before medication was taken by the patient and there was no actual administration

☐ Unknown

3. Which stage of the medication process did the medication error occur?

☐ Prescribing ☐ Preparation for administration

☐ Dispensing ☐ Administration

☐ Transcription ☐ Unknown

☐ Other, please specify: _____

4. Please provide start and stop dates of the occurrence of the medication error:

Start date: _____ Stop date: _____

Cumulative dose: _____mg in _____minutes

5. Where did the error occur:

☐ Patient's home ☐ At Hospital

☐ In public ☐ At school

☐ With First Responders ☐ Unknown

☐ Other, please specify:_____

6. Were there any contributing factors that may have played a part in the origin or the development of the medication error?

a. Patient factors (e.g. poor adherence, cognitive decline, impaired vision, polymedication, first - users).

Please specify: _____

b. Healthcare professional factors (e.g. not accustomed to EURneffy):

☐ Human factor: Mix up with other products (e.g. identification incidents due to similarity of appearance of other products)

☐ Organisational (prepared boxes/packaging, lack of training, transition of patient care)

☐ External factors beyond the control of the healthcare professional or patient (e.g. defective device)

☐ Other - please specify:_____

☐ Unknown

C. Details of any Adverse Reaction(s) (side effects) – only complete this section if an adverse reaction (side effect) was experienced

Was there an adverse drug reaction (side effect) experienced as a consequence of the medication error?

☐ Yes

☐ No

☐ Unknown

Please specify what adverse reactions occurred:_____

Outcome:

☐ Recovered ☐ Resolved with sequelae

☐ Recovering ☐ Fatal

☐ Continuing ☐ Unknown

Do you consider the reaction to be serious?

☐ Yes ☐ No

If yes, please indicate why (tick all that apply):

☐ Patient died due to reaction

☐ Involved or prolonged an inpatient hospitalization

☐ Life threatening

☐ Involved persistent or significant disability

☐ Congenital anomaly/birth defect

☐ Medically significant/Required intervention to prevent one of the above

please specify:_____

Action taken with the medicinal product as result of the medication error:

☐ Drug Withdrawn ☐ Dose not changed

☐ Dose Reduced ☐ Other. Please specify_____

☐ Unknown

Was the reaction related to the suspect drug?

☐ Yes ☐ No

D. Short narrative with (additional) relevant information (including concurrent medical conditions and test results):

Reporter Details (to be included as per company policy):

Name_____

Address_____

Email _____

Phone, Fax_____

[Only those questions from the form should be sent to the reporter which ask for information not yet provided in the initial report. Alternatively, the reporter should be provided with a pre-filled form already including the information initially provided.]

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Details of the proposed additional risk minimisation measures are as follows:

Training devices

This training device is an air-filled, disposable demonstration device to help physicians and patients appreciate firsthand the feel and size of EURneffy, and to practice the correct use of the device. The demonstration devices do not contain active drug and are intended for one-time use.

While these demonstration devices cannot be reused once deployed, they can still be shown to patients and caregivers to demonstrate how to hold EURneffy.

In order to minimise the risks of medication errors, the key element is that the training device is an exact physical replica of EURneffy to accurately simulate the correct handling and actuation of the device.

The target audience is the prescriber and patient/user.

Training videos

Training videos will be made available to physicians, patients and caregivers, to allow prescribers, patients and caregivers to view how to properly administer the product. Self-administration by adult and adolescent, and caregiver administered videos will be made available to address the different scenarios for administration of the product.

To minimise the risks of medication errors, key elements include information communicated in a patient friendly manner as follows:

- Indications in which EURneffy should be used.
- Each EURneffy device contains a single dose of epinephrine and cannot be reused.
- The importance of always carrying two EURneffy devices since there are times when a second dose may be needed.
- Step by step instructions on the correct handling and use of the EURneffy device.
- The importance of seeking medical assistance.
- Advice to read the Instructions for Use (IFU) and to read the Instructions for Use that comes with EURneffy before use, in addition to watching the video.
- Step-by-step instructions that outline the IFU.

The target audience are physicians, caregiver, and the patient/user. The videos will be made available using links on the product website. The step-by-step IFU video will be made available by way of scanning a QR code on the blister and carton labels, as well as a link on the product website.

Digital educational material

A digital patient education brochure with an anaphylaxis/severe allergic reaction action plan will be available.

Patient education brochure will provide patients with information on:

- What EURneffy is.

- How to use EURneffy.
- The most important information that patients should know about using EURneffy as follows:
    - Correct holding, position and actuation of the device.
    - Appropriate guidance for actions post-use of EURneffy (seek medical assistance and monitor patient symptoms).
    - How to identify a serious allergic reaction.

The target audience is the patient/user. The digital educational material will be a pdf document that will be made available via links on the product website.

IFU packaged within the blister containing the EURneffy device

The IFU will be packaged within the EURneffy blister.

This will ensure that in the event that the Patient Information Leaflet is not retained with the EURneffy device, patients will have access to the key information on how to use the product.

To minimise risk of medication errors, key elements include:

- Step by step instructions on the correct handling and use of the EURneffy device.
- All important information for correct use and handing of the device is included with both words and pictograms.
- Appropriate guidance is given for actions post-use of EURneffy (seek medical assistance and monitor patient symptoms).

The target audience is the patient/ user. The IFU is made available by being packaged within the EURneffy blister, with the product.

Annex 7 - Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

A list of all significant changes to the Risk Management Plan over time

Version	Approval date Procedure	Change
3.0	27 March 2026 EMA/X/0000248440	There have been no changes to important identified/potential risk, missing information, pharmacovigilance plan, or risk minimisation measures since EMA approval of the first EURneffy EU RMP version 1.3 (DLP 24 -May- 2024). The indication was updated with the 1mg EURneffy line extension to EU RMP version 2.3 (DLP 01-Nov-2024) approved by the European Commission on 27-Mar-2026. Version 2.3 has been updated to version 3.0 with only change being the version number, proposed text in Table Part I.1 – Product Overview updated to current text, and addition of a list for all significant changes to the Risk Management Plan over time in Annex 8.

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