# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

EURneffy 2 mg nasal spray, solution in single-dose container

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose container delivers adrenaline (epinephrine) 2 mg in 100 microlitres.

Excipients with known effect

Benzalkonium chloride 40 micrograms per single-dose container.
Sodium metabisulfite 5 micrograms per single-dose container.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Nasal spray, solution.

The solution is clear and colourless to pink brownish.

A solution with a pH of 3.0-5.5 and an osmolality of 325–560 mOsm/kg.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

EURneffy is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) due 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 with a body weight ≥ 30 kg.

## 4.2 Posology and method of administration

Posology

This medicinal product should be administered at the first sign of a severe Type I allergic reaction.

The recommended initial dose is a single nasal administration of 2 mg adrenaline.

A dose of 2 mg by nasal administration results in adrenaline plasma concentrations that are within the overall range of exposures observed with devices that deliver 0.3 mg of adrenaline by intramuscular injection in the thigh (see section 5.2).

The patient should be advised to use EURneffy without delay if anaphylaxis is suspected, even if in doubt about the severity of the reaction. They should also be advised to immediately seek emergency medical assistance (dial 999) as they might need further treatment for their anaphylaxis.

In the absence of clinical improvement after 5 minutes, or if deterioration occurs or symptoms reappear after the initial treatment, a second dose should be administered in the same nostril. A maximum of 4 mg (two doses) may be given unless instructed by a medical professional to give additional doses. It is recommended that patients should always carry two nasal sprays to treat an allergy emergency.

*Elderly*

No pharmacokinetic (PK) data are available after nasal administration of adrenaline in patients aged 65 years or older. No dose adjustment is required.

*Paediatric population*

The recommended posology in children with a body weight ≥ 30 kg is the same as adults.

The safety and efficacy of EURneffy in children below 30 kg body weight have not been established. No data are available.

Method of administration

For nasal use only.

This medicinal product is a ready-to-use, nasal spray, solution in single-dose container. It delivers its entire dose upon activation. The nasal spray should not be primed and should not be sprayed in the eyes or mouth.

This medicinal product is for single use only and must be discarded and replaced immediately after use as it delivers only one dose.

*Instructions for administration*

Patients and caregivers should be counselled to carefully read the instructions for use in the package leaflet for complete directions on how to properly administer this medicinal product (see section 4.4).

The patient/caregiver should be informed to seek emergency medical assistance (dial 999) immediately as they might need further treatment for their anaphylaxis.

- If symptoms get worse or reoccur after 5 minutes, or in case of any error in administration , a new EURneffy nasal spray should be used to give a second dose in the same nostril.

- If a second dose is needed but not available, seek emergency medical assistance immediately.

- Patients should lie flat with feet elevated but can gently sit up if they have breathing difficulties. Patients should not change position suddenly and should lie down again as soon as possible. Patients should not stand up even if someone encourages them to. Patients should stay lying down even if they feel better. Pregnant women should lie on their left side. Unconscious patients should be placed on their side in a recovery position.

For full instructions on the use of the medicinal product, see section 6.6.

## 4.3 Contraindications

None.

## 4.4 Special warnings and precautions for use

Instructions for patients at the time of prescribing

A physician who prescribes this medicinal product should take appropriate steps to ensure that the patient understands the indication and use of the nasal spray thoroughly. The physician should review the patient information leaflet and operating instructions of the nasal spray with the patient. All patients who are prescribed this medicinal product should be clearly instructed on how and when to use the product (see section 4.2). It is strongly advised to also educate the patient's immediate associates (e.g. parents, caregivers, teachers) on the correct use of this medicinal product in case support is needed in an emergency.

For children under 12 years of age, the caregiver should administer EURneffy or determine that the child is properly instructed in the use of EURneffy and is fully capable of administration themselves.

Patients with a cold or a congested nose can use this medicinal product, even in these conditions, however the PK profile may be different (see section 5.2).

Warnings for patients about anaphylaxis

Patients should be instructed to recognise symptoms of severe allergic reactions and anaphylaxis that may occur within minutes after exposure and which may 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. Patients with concomitant asthma may be at increased risk of severe anaphylactic reaction.

Adrenaline is recommended for use at first signs or symptoms of severe allergic reactions leading to anaphylaxis. Patients should be instructed to always carry adrenaline in situations of potential risks.

The patient/caregiver should be informed about the possibility of biphasic anaphylaxis which is characterised by initial resolution followed by recurrence of symptoms some hours later. The patient should be advised to always seek medical assistance immediately after any severe allergic reaction.

Populations at increased risks with the use of adrenaline

Extreme caution should be taken when administering adrenaline to patients who have a heart disease.

Use of adrenaline with medicinal products that may sensitise the heart to arrhythmias, e.g. digoxin, mercurial diuretics, or quinidine, ordinarily is not recommended (see section 4.5). Anginal pain may be induced by adrenaline in patients with coronary insufficiency.

There is a risk of adverse reactions following adrenaline administration in patients with high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia, and hypokalaemia. In patients with Parkinson's disease, adrenaline may be associated with a transient worsening of Parkinson's symptoms such as rigidity and tremor.

Individuals with hyperthyroidism, cardiovascular disease, hypertension, or diabetes, elderly individuals, and pregnant women may be at greater risk of developing adverse reactions after adrenaline administration (see sections 4.6 and 4.8).

Patients with these conditions, and/or any other persons who might be in a position to administer this medicinal product to a patient experiencing a severe allergic reaction or anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medicinal product should be used.

Excipients with known effect

*Benzalkonium chloride*

This medicinal product contains benzalkonium chloride that may cause irritation or swelling inside the nose, especially if used for a long time.

*Sodium metabisulphite*

This medicinal product contains metabisulphite that may rarely cause severe hypersensitivity reactions and bronchospasm.

## 4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline and other medicinal products

Caution is indicated in patients receiving medicinal products that may sensitise the heart to arrhythmias, including digoxin, mercurial diuretics (e.g. chlormerodrin, merbaphen, mersalyl acid, meralluride, mercaptomerin, mercurophylline, merethoxylline procaine) or quinidine.

The effects of adrenaline may be potentiated by tricyclic antidepressants (e.g. imipramine) and mono amine oxidase inhibitors (MAO-inhibitors) (e.g. isocarboxazid, phenelzine, selegiline, tranylcypromine) and catechol-O-methyl transferase inhibitors (COMT-inhibitors) (e.g. entacapone, tolcapone, carbidopa-levodopa-entacapone, opicapone), thyroid hormones, theophylline, oxytocin, parasympatholytics (e.g. atropine, cyclopentolate, homatropine, hyoscine, tropicaminde), certain antihistamines (diphenhydramine, chlorpheniramine), levodopa, and alcohol.

Pressor effects of adrenaline

Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic-blocking medicinal products such as phentolamine.

Adrenaline and insulin

Adrenaline inhibits the secretion of insulin, thus increasing the blood glucose level. It is unlikely if given in an acute emergency that adrenaline would have any persistent effect on blood glucose levels, but for diabetic patients receiving adrenaline it may be necessary to increase their dose of insulin or oral hypoglycaemic medicinal products.

Adrenaline and beta-blocking medicinal products

The beta-stimulating effect of adrenaline may be inhibited by simultaneous treatment with beta-blocking medicinal products, e.g. propanolol.

## 4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data on the effect of EURneffy in pregnant women.

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicates no malformation or feto/neonatal toxicity of adrenaline. While an endogenous substance and blood levels after administration of EURneffy are within normal physiologic ranges, adrenaline increases blood pressure and heart rate which can impact the foetus.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of this medicinal product may be considered during pregnancy, if necessary.

Breastfeeding

There are no data on the effect of adrenaline in breastfeeding women. However, EURneffy can be used in breastfeeding women.

It is unknown whether adrenaline/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded. However, due to its poor oral bioavailability and short half-life, exposure is expected to be very low in the breastfed infants.

Fertility

There are no data on the effect of EURneffy on human fertility.

Adrenaline is an endogenous substance and blood levels after administration of EURneffy are within normal physiological ranges and as such it is unlikely that there would be any detrimental effects on fertility.

## 4.7 Effects on ability to drive and use machines

EURneffy has no or negligible influence on the ability to drive and use machines. It is not recommended that patients who are experiencing an anaphylactic reaction drive or use machines because of the anaphylactic reaction.

## 4.8 Undesirable effects

Summary of safety profile

The most frequently occurring adverse reactions (very common events ≥ 10%) observed in clinical studies of EURneffy were reported only after second 2 mg dose (4 mg total) and include throat irritation (18.8%), headache (17.6%), nasal discomfort (12.9%) and feeling jittery (10.6%). None of the adverse drug reactions observed in the clinical studies were serious.

Tabulated list of adverse reactions

Adverse reactions are summarised based on analysis of pooled safety data from primary PK/pharmacodynamic (PD) studies using EURneffy 2 mg in adult healthy volunteers, in patients with Type 1 allergies and in patients with allergic rhinitis. The adverse reactions are ranked according to system organ class and frequency according to the following convention:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)

- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (frequency cannot be estimated from the available data)

**Table 1: Adverse drug reactions identified with EURneffy**

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Psychiatric disorders | Common | Anxiety |
| | Uncommon | Euphoric mood<br>Nervousness |
| | Not known | Disorientation[1]<br>Memory impairment[1]<br>Panic reaction[1] |
| Nervous system disorders | Very common | Headache |
| | Common | Tremor |
| | Uncommon | Dizziness<br>Paraesthesia<br>Head discomfort<br>Presyncope |
| | Not known | Psychomotor hyperactivity[1]<br>Somnolence[1] |
| Eye disorders | Uncommon | Lacrimation increased |
| Cardiac disorders | Common | Palpitations |
| | Not known | Angina[1]<br>Cardiac arrhythmias[1,2]<br>Stress cardiomyopathy[1]<br>Tachyarrhythmia[1]<br>Tachycardia[1]<br>Ventricular ectopy[1] |
| Vascular disorders | Not known | Hypertension[1]<br>Vasoconstriction[1] |
| Respiratory, thoracic, and mediastinal disorders | Very common | Nasal discomfort<br>Throat irritation |
| | Common | Rhinorrhoea<br>Nasal oedema<br>Rhinalgia<br>Nasal congestion |
| | Uncommon | Oropharyngeal pain<br>Nasal pruritus<br>Sneezing<br>Intranasal paraesthesia<br>Paranasal sinus discomfort<br>Epistaxis<br>Nasal dryness<br>Nasal mucosal disorder |

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Gastrointestinal disorders | Uncommon | Nausea<br>Paresthesia oral<br>Salivary hypersecretion<br>Toothache<br>Gingival discomfort |
| Skin and subcutaneous tissue disorders | Uncommon | Pruritus |
| | Not known | Paraesthesia[1] |
| General disorders and administration site conditions | Very common | Feeling jittery |
| | Uncommon | Chest discomfort<br>Energy increased<br>Fatigue<br>Feeling hot |
| Investigations | Common | Blood pressure increased<br>Heart rate increased |
| | Uncommon | Body temperature increased |

[1] Adverse reactions that have not been observed in clinical studies with EURneffy, but are known to occur with other adrenaline formulations including intravenous, intramuscular, and subcutaneous administrations.

[2] Cardiac arrhythmias may follow administration of adrenaline (see section 4.4).

Paediatric population

In a clinical trial of paediatric subjects, 16 subjects between 8 and 17 years of age weighing more than 30 kg were treated with EURneffy 2 mg. The most common adverse reactions included: nasal discomfort and intranasal paraesthesia (25.0%); sneezing (18.8%); fatigue, feeling jittery, paraesthesia, rhinalgia, and rhinorrhoea (12.5%); and epistaxis, lacrimation increased, oropharyngeal pain, and pharyngeal paraesthesia (6.3%).

There were no clinically relevant differences in the safety between the paediatric and adult populations treated with EURneffy 2 mg.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Symptoms

Overdose of adrenaline may cause severe headaches, chest pain, dizziness, nausea, and blurred vision. Significant overdoses or injection into a blood vessel can also cause cerebral haemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary oedema because of peripheral vascular constriction together with cardiac stimulation.

Management

Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking medicinal products.

If an adrenaline overdose induces pulmonary oedema that interferes with respiration, treatment consists of a rapidly acting alpha-adrenergic blocking medicinal product such as phentolamine and/or intermittent positive-pressure respiration.

Adrenaline overdose can cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Treatment of arrhythmias may consist of administration of beta-adrenergic blocking medicinal products.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, adrenergic and dopaminergic agents

ATC code: C01CA24

Mechanism of action

Adrenaline is a nonselective agonist of all adrenergic receptors, including alpha- and beta-adrenergic receptors. Binding to these receptors triggers a number of actions of sympathetic nerve system.

Pharmacodynamic effects

Through its action on alpha-adrenergic receptors, adrenaline lessens histamine induced vasodilation. Adrenaline also reduces the vascular permeability induced by histamine that occurs during anaphylaxis.

Adrenaline, through its action on beta-adrenergic receptors in bronchial smooth muscle, causes bronchial smooth muscle relaxation.

Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

Clinical efficacy

Four clinical pharmacology studies of EURneffy in adults and one clinical pharmacology study in paediatric subjects who weigh 30 kg or more are described below.

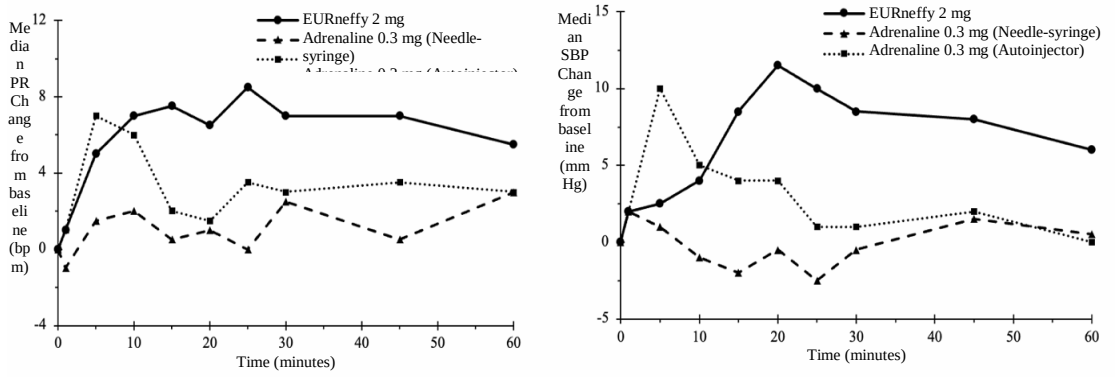
*Systolic blood pressure and pulse rate in healthy adult subjects (Study EPI 15)*

Study EPI 15 was conducted in healthy adult subjects (N=42) that compared the PK and PD (i.e. pulse rate (PR) and systolic blood pressure (SBP)) of adrenaline following:

- One nasal dose of EURneffy 2 mg to one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product and an auto-injector product).
- Two nasal doses of EURneffy 2 mg, administered 10 minutes apart, into either same naris or opposite nares to two intramuscular doses of adrenaline injection 0.3 mg (using an auto-injector) administered 10 minutes apart.

Results following one dose of all adrenaline products demonstrated an increase from baseline SBP and PR as shown in Figure 1.

**Figure 1: Median pulse rate (PR) and systolic blood pressure (SBP) change from baseline following one dose of adrenaline in healthy subjects [Study EPI 15]**




Results following two nasal doses of EURneffy (in the same naris or opposite nares) in comparison to two intramuscular doses of adrenaline injection (using an auto-injector) showed a similar trend in median/mean SBP and PR responses.

*SBP and PR in adult patients with Type I allergy without anaphylaxis (Study EPI 17)*

Study EPI 17 was conducted in adult patients with Type I allergy without anaphylaxis (N=42) that compared the PK and PD of adrenaline following self-administered one nasal dose of EURneffy 2 mg to staff-administered one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product). In Study EPI 17, SBP and PR responses were assessed as a change from baseline over 60 minutes. The SBP and PR responses results in Study EPI 17 were similar to those demonstrated in Study EPI 15.

*SBP and PR in adult patients with allergic rhinitis (Study EPI 16 and EPI 18)*

Study EPI 16 and Study EPI 18 were conducted in adult subjects with seasonal allergic rhinitis outside of the allergy season. Subjects were required to have seasonal allergic rhinitis which was confirmed with a nasal allergen challenge (NAC) during screening and did not have any allergy symptoms prior to treatment. Allergic rhinitis symptoms were induced by spraying the known allergen into the subject's nostrils in which a minimum total nasal symptom score of ≥ 5 out of 12, with a congestion component of ≥ 2 out of 3 had to be reached.

Study EPI 16 enrolled 36 subjects. In this cross-over study, subjects received adrenaline as each of the following:

- One nasal dose of EURneffy 2 mg without NAC.
- One nasal dose of EURneffy 2 mg after undergoing NAC to induce rhinitis/nasal congestion.
- One intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product) without NAC.
- One intramuscular dose of adrenaline injection 0.5 mg (using a needle-syringe product) without NAC.

In Study EPI 16, SBP and PR responses were assessed as a change from baseline over 60 minutes. Results showed the following:

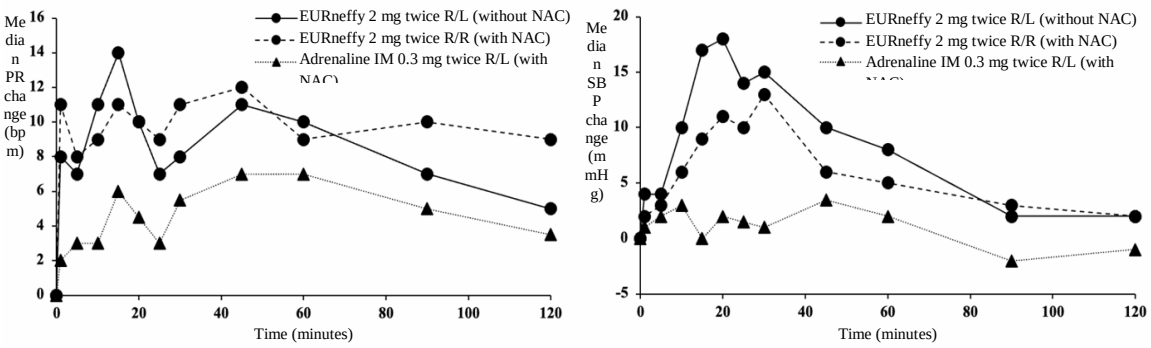
- Median SBP and PR for EURneffy with NAC initially increased from baseline, but the median responses were lower than the use of EURneffy without NAC after 5 to 15 minutes post-dose.
- Median SBP response for EURneffy with NAC was initially higher than the median SBP response for the intramuscular adrenaline injection without NAC through 20 minutes, after which the median SBP response for EURneffy with NAC became comparable to the adrenaline injection without NAC through 60 minutes post-dose.
- Median PR response for EURneffy with NAC was initially higher than adrenaline injection without NAC during the first 5 minutes post-dose, but then was numerically lower than the median PR response for adrenaline injection without NAC through 60 minutes post-dose.

Study EPI 18 enrolled 43 subjects. In this cross-over study, subjects received two doses of adrenaline administered 10 minutes apart as each of the following:

- Two nasal doses of EURneffy 2 mg (in the opposite nares (right(R)/left (L)) without NAC.
- Two intramuscular doses of adrenaline injections 0.3 mg (using a needle-syringe product; in the opposite thigh (R/L)) without NAC.
- Two nasal doses of EURneffy 2 mg (either in the same naris (R/R) or opposite nares (R/L)) after NAC to induce allergic rhinitis/nasal congestion.
- Two intramuscular doses of adrenaline injections 0.3 mg (using a needle-syringe product; in the opposite thigh (R/L)) after NAC to induce allergic rhinitis/nasal congestion.

In Study EPI 18, SBP and PR responses were assessed as a change from baseline over 60 minutes. Results showed the following:

**Figure 2: Median change from baseline for systolic blood pressure (SBP) and pulse rate (PR) following two doses of adrenaline administered 10 minutes apart in right and left nares (R/L) or right and right nares (R/R) in subjects with allergic rhinitis with and without nasal allergen challenge (NAC) [Study EPI 18]**




Paediatric population

*SBP and PR in paediatric patients with Type I allergy without anaphylaxis (Study EPI 10)*

Study EPI 10 was a single-arm study conducted in paediatric patients who weighed 30 kg or more (age range: 8 to 17 years) with Type I allergy without anaphylaxis (N=21) that assessed the PK and PD of adrenaline following one nasal dose of EURneffy 2 mg. The median change in SBP and PR from baseline over the 60 minutes post-dose were numerically lower than in healthy adults who received the same dose of EURneffy in Study EPI 15.

The MHRA has deferred the obligation to submit the results of studies with EURneffy in one or more subsets of the paediatric population in the treatment of allergic reactions (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Following one nasal dose of EURneffy 2 mg, the geometric mean plasma adrenaline concentration-time profile was overall within the range of that following one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product and an auto-injector) 60 minutes post-dose. The integrated PK parameters of adrenaline are summarised in table 2.

**Table 2: Mean (CV%) and geometric mean plasma PK parameters following one or two doses of adrenaline (integrated analysis)**

| Treatment | N | $t_{max}$ (min) median (range) | $C_{max}$ (pg/mL) | | $AUC_{last}$ (min*pg/mL) | |
|---|---|---|---|---|---|---|
| | | | Mean (%CV) | Geo.mean | Mean (%CV) | Geo.mean |
| EURneffy 2 mg (HCP administration) | 78 | 20.5 (2 - 150) | 485 (70.6) | 361 | 40900 (67.5) | 32600 |
| EURneffy 2 mg (self-administration) | 32 | 30 (10 - 240) | 448 (67.1) | 342 | 50365 (55.5) | 41077 |
| EURneffy 2 mg (paediatrics) | 16 | 25.0 (2.5 - 120) | 540 (70.7) | 433 | 35500 (76.3) | 27800 |
| EURneffy 2 mg twice (L/R) | 39 | 30 (6 - 150) | 1000 (93.1) | 706 | 86000 (77) | 66700 |
| EURneffy 2 mg twice (R/R) | 39 | 30 (4 - 150) | 992 (75.3) | 729 | 86500 (60.5) | 69900 |
| Adrenaline 0.3 mg IM | 178 | 45 (3.9 -360) | 277 (65.4) | 234 | 27900 (38.7) | 26100 |
| Adrenaline 0.3 mg IM twice | 70 | 45 (6 - 180) | 436 (48.8) | 386 | 47500 (32.6) | 45300 |
| EpiPen 0.3 mg | 77 | 10 (2 - 45) | 581 (75.6) | 447 | 31600 (39.3) | 29200 |
| EpiPen 0.3 mg twice | 78 | 20 (4 - 360) | 754 (64.7) | 630 | 55000 (47.9) | 29200 |

AUC: area under the curve; $C_{max}$: the maximum observed concentration; CV: coefficient of variation; Geo. mean: geometric mean; HCP: healthcare professional; IM: intramuscular; L: left; N: number of subjects; R: right, $t_{max}$: the time it takes to reach the $C_{max.}$

Geometric mean plasma adrenaline concentrations during the first 60 minutes post-dosing compared to adrenaline 0.3 mg and 0.5 mg administered by intramuscular injection are summarised in Table 3.

**Table 3: Geometric mean plasma PK parameters following one dose of adrenaline in healthy subjects (EURneffy compared to 0.3 mg and 0.5 mg intramuscular injection)**

| Treatment | N | $t_{max}$ (min) median | $C_{max}$ (pg/mL) | AUC (min*pg/mL) | | | |
|---|---|---|---|---|---|---|---|
| | | | | $AUC_{0-10min}$ | $AUC_{0-20min}$ | $AUC_{0-45min}$ | $AUC_{0-60min}$ |
| EURneffy 2 mg | 78 | 20 | 361 | 719 | 2640 | 8140 | 10700 |
| Adrenaline 0.3 mg IM | 178 | 45 | 234 | 627 | 1520 | 5260 | 7820 |
| Adrenaline 0.5 mg IM | 123 | 45 | 335 | 681 | 1840 | 7250 | 11300 |

AUC: area under the curve; $C_{max}$: the maximum observed concentration; IM: intramuscular; N: number of subjects; $t_{max}$: the time it takes to reach the $C_{max}$

Adrenaline has a rapid onset of action after administration. Following nasal administration to healthy volunteers, adrenaline was rapidly absorbed after both single and repeated dosing, with a time to maximum plasma concentration in 20 to 30 minutes. In subjects with rhinitis (congestion and nasal oedema), adrenaline is absorbed more rapidly with the maximum concentration observed in about 10 minutes.

Biotransformation

Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).

Elimination

Much of a dose of adrenaline is excreted as metabolites in urine. Elimination is mainly via metabolism of the liver and sympathetic nerve endings, with a small amount excreted unchanged in the urine. The plasma half-life following nasal administration is about 2 to 3 minutes.

Paediatric population

*Paediatric patients with Type I allergies without anaphylaxis (Study EPI 10)*

In paediatric patients with Type I allergies weighing 30 kg or more (age range: 8 to 17 years), following a single 2 mg nasal dose of EURneffy, the geometric mean plasma adrenaline concentration time profile was similar to that of healthy adults receiving the same dose within about 15 minutes post-dose (in a different study) and then became slightly higher than that of healthy adults (see table 2).

### 5.3 Preclinical safety data

Nonclinical data carried out on EURneffy formulation and on adrenaline based on scientific literature, reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride

Dodecylmaltoside

Disodium edetate

Benzalkonium chloride

Sodium metabisulphite (E 223)

Hydrochloric acid, concentrated (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injections

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

30 months.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

If accidentally frozen, the nasal spray will not function. Allow the nasal spray to thaw at least one hour; do not use if the contents are still frozen or not completely thawed. Freezing does not affect the shelf life of the product.

## 6.5 Nature and contents of container

Type I glass vials closed with a grey bromobutyl rubber stopper and then assembled into a unit

dose sprayer device. The device is a non-pressurised dispenser delivering a single-dose nasal spray.

Pack size: Pack of 2 single-dose nasal sprays

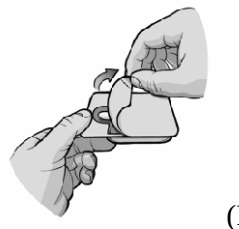
Pack of 1 single-dose nasal spray

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Instructions for use

A: To administer, the nasal spray should be removed from the packaging, by pulling open the packaging (see figure 1A).



(Figure 1A)

B: Hold the nasal spray with your thumb on the bottom of the plunger and a finger on either side of the nozzle (see figure 1B).

- Do not pull or push on the plunger.
- Do not test or pre-spray; each nasal spray has only one dose.

(Figure 1B)

C: Insert tip of nasal spray into a nostril until your fingers touch your nose (see figure 1C).

- Keep the nozzle straight into the nose pointed toward your forehead.
- Do not angle the nasal spray to the inner or outer walls of the nose.

(Figure 1C)

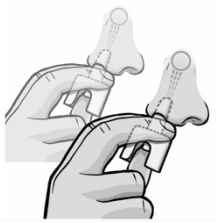
D: Press plunger up firmly until it snaps up and sprays into the nostril (see figure 1D).

(Figure 1D)

Do not angle the nasal spray to the inner or outer walls of the nose.

Use EURneffy without delay if a severe allergic reaction (anaphylaxis) is suspected, even if in doubt about the severity of the reaction. Seek emergency medical assistance immediately (dial 999) as you might need further treatment for your anaphylaxis.

If symptoms continue to worsen or reoccur after 5 minutes, or in case of any error in administration, use a new EURneffy nasal spray to give a second dose in the same nostril as the first dose.



If accidentally frozen, the nasal spray will not function. Allow the nasal spray to thaw at least one hour; do not use if the contents are still frozen or not completely thawed. Freezing does not affect the shelf life of the product.

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

## 7 MARKETING AUTHORISATION HOLDER

ALK-Abelló A/S

Bøge Allé 6-8

2970 Hørsholm

Denmark

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 10085/0060

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