▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
neffy® ADRENALINE (EPINEPHRINE) NASAL SPRAY

1 NAME OF THE MEDICINE
Adrenaline (epinephrine)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single-dose *neffy* nasal spray delivers adrenaline (epinephrine) 1 mg or 2 mg in one spray (100 microlitres) of solution.

Excipients with known effect: Contains sulfites.
Contains 0.4 mg benzalkonium chloride in one spray (100 microlitres).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM
neffy is an aqueous solution, filled into a glass vial with bromobutyl rubber stopper. The vial is enclosed in a white polypropylene holder which forms part of the single-dose nasal spray.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

neffy is indicated for emergency treatment of type I allergic reactions, including anaphylaxis, in adults and children aged 4 years and older and weighing 15 kg or greater.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dosage

Patients weighing 15 kg to less than 30 kg: The recommended dosage is one spray of *neffy* 1 mg (1 mg of adrenaline) administered into one nostril.

Patients weighing 30 kg or greater: The recommended dosage is one spray of *neffy* 2 mg (2 mg of adrenaline) administered into one nostril.

Anaphylaxis is a life-threatening emergency and self-administration of adrenaline is not intended as a substitute for immediate medical care. The patient should be advised to seek emergency medical

assistance immediately following administration of *neffy* for close monitoring of the anaphylactic episode and in the event further treatment is required.

In the absence of clinical improvement, or if deterioration occurs or symptoms reappear after 5 minutes following the initial treatment, a second dose should be administered, using a new *neffy* nasal spray (ideally in the same nostril). It is recommended that patients should always carry two *neffy* nasal sprays in case of severe allergic reaction. More than two sequential doses of adrenaline should be administered under direct medical supervision.

Method of administration

For nasal use only.

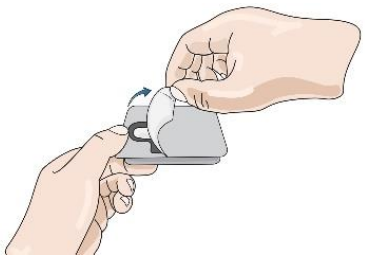
neffy is a ready-to-use, single-dose, nasal spray. It delivers its entire dose upon activation. **The nasal spray should not be primed** and should not be sprayed in the eyes or mouth.

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

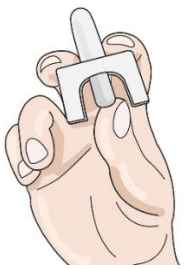
Instructions for administration

Patients and caregivers should be counselled to carefully read the instructions for use for complete directions on how to properly administer this medicinal product.

To administer, remove the *neffy* nasal spray from the packaging, by pulling open the packaging as shown.

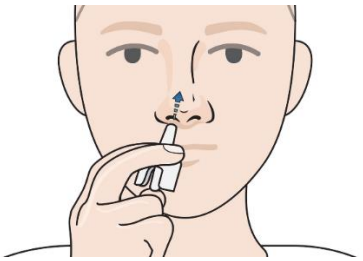


1. Hold the nasal spray with your thumb on the bottom of the plunger and a finger on either side of the nozzle (see Figure 1).
    - Do not pull or push on the plunger.
    - **Do not test or pre-spray**; each nasal spray has only one dose.



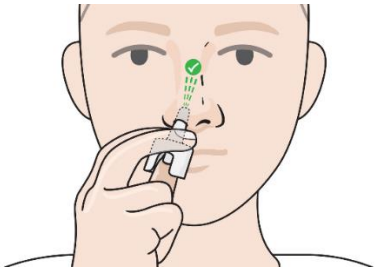
(Figure 1)

2. Place the nozzle of the nasal spray into a nostril until fingers touch the nose (see Figure 2). For smaller nostrils, aim for fingers to touch the nose.
    - Keep the nozzle pointed toward the forehead.
    - Do not angle the nasal spray to the inner or outer walls of the nose.



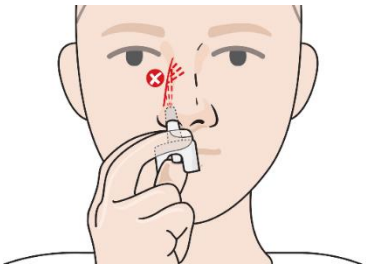
(Figure 2)

3. Press plunger up firmly until it sprays into the nostril (see Figure 3).



(Figure 3)

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



Seek emergency medical assistance immediately following administration of *neffy* for close monitoring of the anaphylactic episode and in the event further treatment is required.

In the absence of clinical improvement, or if deterioration occurs or symptoms reappear after 5 minutes following the initial treatment, a second dose should be administered, using a new *neffy* nasal spray (ideally in the same nostril).

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Instructions for patients at the time of prescribing

The prescribers of this medicinal product should take appropriate steps to ensure that the patient understands the indication and use of the nasal spray thoroughly. The prescriber 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 DOSE AND METHOD OF ADMINISTRATION).

It is strongly advised that the patient's immediate associates (e.g., parents, caregivers, teachers) are also educated 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 *neffy* or determine that the child is properly instructed in the use of *neffy* and is fully capable of administration themselves.

Patients with a cold or a congested nose can use this medicinal product, however, the pharmacokinetic profile may be different (see Section 5.2 PHARMACOKINETIC PROPERTIES).

No data are available regarding the use of *neffy* in patients with underlying structural and anatomical nasal conditions.

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 allergy events leading to anaphylaxis. Patients should be instructed to carry adrenaline at all times.

Anaphylaxis is a life-threatening emergency and self-administration of adrenaline is not intended as a substitute for immediate medical care. The patient should be advised to seek emergency medical assistance immediately following administration of *neffy* for close monitoring of the anaphylactic episode and in the event further treatment is required.

Populations at increased risks with the use of adrenaline

Some patients may be at greater risk for developing adverse reactions after adrenaline administration. Despite these concerns, it should be recognised that the presence of these

conditions is not a contraindication to adrenaline administration in an acute, life-threatening situation.

Caution should be taken when administering adrenaline to patients who have a heart disease including patients with cardiac arrhythmias, coronary artery disease, or hypertension. In such patients, or in patients who are on drugs that may sensitise the heart to arrhythmias, adrenaline may precipitate or aggravate angina, as well as produce ventricular arrhythmias (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 Section 4.6 FERTILITY, PREGNANCY AND LACTATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 adrenaline should be used.

Patients with Underlying Structural or Anatomical Nasal Conditions

Clinical pharmacology studies with *neffy* included subjects with history of allergic rhinitis, but did not include subjects with underlying structural and anatomical nasal conditions (e.g., polyps, history of nasal fractures or injuries, or history of nasal surgery). The effect of these conditions on the absorption of *neffy* is unknown. Careful consideration should be given to the appropriateness of *neffy* for these patients.

Allergic Reactions Associated with Sulfite

Adrenaline is the preferred treatment for serious allergic or other emergency situations even though *neffy* contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using adrenaline in a life-threatening situation may not be satisfactory. The presence of a sulfite in *neffy* should not deter administration of the drug for treatment of serious allergic reactions including anaphylaxis.

Use in the elderly

No data after nasal administration of adrenaline are available. No dose adjustment is required. Elderly patients may be at a greater risk of developing adverse reactions after adrenaline administration, however, this should not deter administration of *neffy* for treatment of serious allergic reactions including anaphylaxis. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Paediatric use

The safety and effectiveness of *neffy* for emergency treatment of type I allergic reactions, including anaphylaxis, have not been established in paediatric patients who weigh less than 15 kg. No children less than 4 years of age were included in the clinical trials for *neffy*.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Central nervous system and other medicinal products

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

Caution is indicated in patients receiving medicinal products that may sensitise the heart to arrhythmias, including digoxin or quinidine.

Other sympathomimetic medicinal products

Adrenaline should not be administered with other sympathomimetic agents because of the danger of additive effects and increased toxicity.

Alpha-adrenergic blocking agents

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

Hypoglycaemic medicinal products

Adrenaline inhibits the secretion of insulin, thus increasing the blood glucose level. It is unlikely if given in an acute emergency situation 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.

Beta-adrenergic blocking agents

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

Effects on fertility

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

fertility. This should not prevent the use of adrenaline under the conditions noted under Section 4.1 Therapeutic Indications.

Use in pregnancy – Pregnancy Category A

Adrenaline has been given to a large number of pregnant woman and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Adrenaline may delay the second stage of labour by inhibiting contractions of the uterus.

Use with caution in pregnant women whose maternal blood pressure is in excess of 130/80 mmHg.

As there are risks to the mother and fetus associated with anaphylaxis, treatment with adrenaline should not be delayed.

Use in lactation

There are no data on the effect of adrenaline in breast feeding mothers. However, *neffy* can be used in breast feeding mothers.

Due to its poor oral bioavailability and short half-life, exposure is expected to be very low in the breastfed infants. Treatment for anaphylaxis in breastfeeding patients should not be delayed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

It is not recommended that patients who are suffering an anaphylactic reaction drive or use machines because of the anaphylactic reaction.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

There were no very common adverse reactions (≥ 10%) observed in clinical trials following a single dose of *neffy* 2mg. The most frequently occurring adverse reactions (very common events ≥ 10%) observed in clinical studies of *neffy* were reported only after two 2 mg doses (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 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/PD studies using *neffy* 2 mg in adult healthy volunteers, in patients with Type 1 allergies and in patients with allergic rhinitis following either one or two doses. 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 *neffy* 2 mg following either 1 or 2 doses.

System Organ Class	Frequency	Adverse Reaction
Psychiatric disorders	Common	Anxiety
	Uncommon	Euphoric mood Nervousness
Nervous system disorders	Very Common	Headache
	Common	Tremor
	Uncommon	Dizziness Paraesthesia Head discomfort Presyncope
Eye disorders	Uncommon	Lacrimation increased
Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very Common	Nasal discomfort Throat irritation
	Common	Rhinorrhoea Nasal oedema Rhinalgia Nasal congestion
	Uncommon	Oropharyngeal pain Nasal pruritus Sneezing Intranasal paraesthesia Paranasal sinus discomfort Epistaxis Nasal dryness Nasal mucosal disorder
Gastrointestinal disorders	Uncommon	Nausea Paresthesia oral Salivary hypersecretion Toothache Gingival discomfort
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
General disorders and administration site conditions	Very Common	Feeling jittery
	Uncommon	Chest discomfort Energy increased Fatigue Feeling hot
Investigations		
	Uncommon	Body temperature increased

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 *neffy* 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 *neffy* 2 mg.

In paediatric patients weighing between 15 kg and < 30 kg in body weight and treated with *neffy* 1 mg, the most common adverse reactions reported were nasal congestion (19%), upper respiratory tract congestion (14%), dry throat (10%), nasal dryness (10%), and paraesthesia (10%).

Adverse Reactions from Post Approval Use of Adrenaline Products

The following adverse reactions have been identified during post approval use of adrenaline and not *neffy* specifically. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: angina, arrhythmias (including fatal ventricular fibrillation), cerebral haemorrhage, hypertension, pallor, tachyarrhythmia, tachycardia, vasoconstriction, ventricular ectopy, and stress cardiomyopathy.

Metabolism and Nutrition Disorders: transient hyperglycemia, sweating

Neurological: disorientation, impaired memory, panic, psychomotor agitation, sleepiness, tingling, weakness

Psychiatric: anxiety, apprehensiveness, restlessness

Respiratory: respiratory difficulties

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 the sympathetic nervous 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, which can lead to a loss of intravascular fluid volume and hypotension.

Adrenaline, through its action on beta-adrenergic receptors in bronchial smooth muscle, causes bronchial smooth muscle relaxation and helps alleviate bronchospasm, wheezing and dyspnoea that may occur during anaphylaxis.

Other major effects are increased systolic blood pressure, reduced diastolic pressure, tachycardia, hyperglycaemia and hypokalaemia. It is a powerful cardiac stimulant raising cardiac rate, cardiac output and coronary circulation. It has vasopressor properties, an antihistaminic action and is a bronchodilator.

Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis due to its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

Clinical trials

Four clinical pharmacology studies of ***neffy*** in adults and one clinical pharmacology study in paediatric subjects who weigh 15 kg or greater are described below.

Adult population

One and two doses of neffy in healthy volunteers (Study EPI 15)

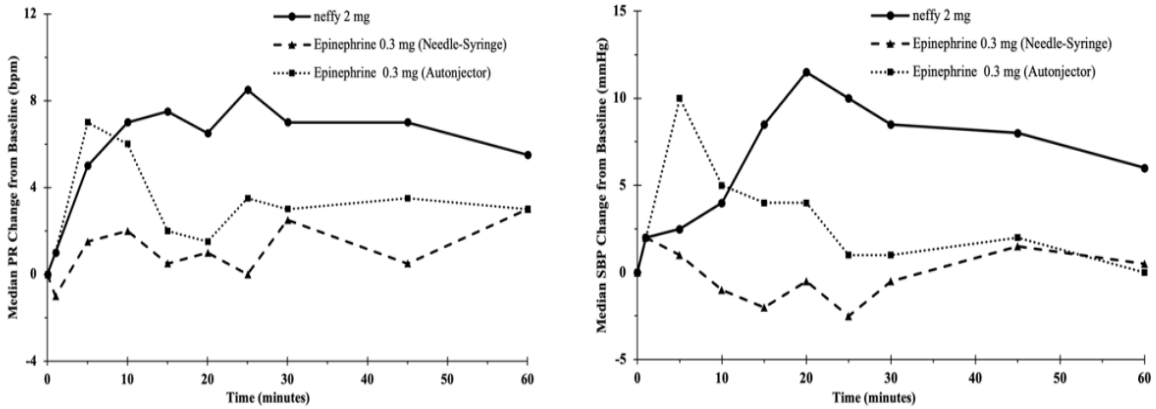
Study EPI 15 was conducted in healthy adult subjects (N=42) that compared the pharmacokinetics (PK) and pharmacodynamics (PD) of adrenaline following:

- One dose of *neffy* 2 mg to one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product and an auto-injector product).

- Two doses of *neffy* 2 mg, administered 10 minutes apart, into either same nostril or opposite nostrils 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 systolic blood pressure (SBP) and pulse rate (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]



The median increase in SBP and PR for *neffy* was within the range of both adrenaline injection treatments during the first 10 minutes post-dose. Thereafter, the median SBP and PR responses for *neffy* were higher than both adrenaline injection treatments through 60 minutes post-dose.

Results following two nasal doses of *neffy* (in the same nostril or opposite nostrils) in comparison to two intramuscular doses of adrenaline injection (using an autoinjector) showed a similar trend in median/mean SBP and PR responses.

Self-administration 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 *neffy* 2 mg to staff-administered one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product). The SBP and PR responses results in Study EPI 17 were similar to Study EPI 15.

Adult patients with allergic rhinitis with and without nasal allergen challenge (Study EPI 16 and EPI 18)

Study EPI 16 (N=36) and Study EPI 18 (N=43) were cross over studies conducted in adult subjects with seasonal allergic rhinitis outside of 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 (TNSS) of ≥ 5 out of 12, with a congestion component of ≥ 2 out of 3 had to be reached. The

comparative PK and PD of *neffy* 2mg and IM 0.3 mg were assessed in subjects both in a normal state and under allergic rhinitis induced by NAC as a single dose (Study EPI 16) and a repeat dose with two doses of adrenaline given 10 minutes apart (Study EPI 18).

After induced allergic rhinitis, ***neffy*** 2mg resulted in more rapid but numerically lower mean SBP and PR response compared to ***neffy*** 2mg under normal nasal conditions. Regardless of nasal conditions (normal or allergic rhinitis), the PD response following *neffy* were comparable or greater than IM adrenaline.

Adult patients with upper respiratory tract infections (Study EPI 14)

Study EPI 14 was a single dose, two period study to understand the impact of nasal oedema and congestion on the absorption of adrenaline administered via *neffy*. Subjects (N=21) were enrolled when they experienced an upper respiratory tract infection (URTI) with nasal congestion and oedema (e.g. flu, common cold, nasal infection). Subjects received *neffy* 2mg when experiencing symptoms and were then instructed to return after they recovered for a second dose of *neffy* 2mg under normal nasal conditions (N=16).

The pharmacodynamic responses observed under URTI conditions were consistent with the observed and expected responses to *neffy* 2mg in other clinical studies. The presence of a URTI did not appear to have any meaningful effect on adrenaline absorption during the first 25 minutes post dose. There were no statistically significant differences in PK parameters.

Paediatric Population

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 15 kg or greater (age range: 4 to 17 years) with type I allergy without anaphylaxis (N=42) that assessed the PK and PD of adrenaline following one dose of *neffy* 1 mg (for subjects who weigh 15 kg to < 30 kg) and 2 mg (for subjects who weigh 30 kg or greater). When compared to adult patients (Study EPI 15 and Study EPI 17), the median change in SBP from baseline over the 60 minutes post-dose were numerically lower than in adults who received *neffy* 2 mg, while the median change in PR from baseline over 60 minutes post-dose was within the range of adults who received *neffy* 2 mg.

Paediatric food allergy patients (Study JP03)

A Phase 3 open-label study was conducted in 15 paediatric food allergy patients (aged 6 to 17 years) in Japan. Anaphylaxis symptoms were induced, followed by administration of *neffy* at the onset of moderate anaphylaxis symptoms. Patients received *neffy* 1 mg (15-30 kg) or 2 mg (≥30 kg). The median time to resolve moderate anaphylaxis symptoms after a single dose of *neffy* was 16 minutes, with no patient requiring a second dose. One patient developed a biphasic reaction after 2 hours and 45 minutes and consequently received intramuscular adrenaline. For both dose groups, the mean total grade started decreasing within five minutes of *neffy* administration (the first assessment timepoint).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adrenaline has a rapid onset of action after administration. Following nasal administration to healthy volunteers, adrenaline was rapidly absorbed after both single and repeat 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.

The pharmacokinetic profile of adrenaline is highly variable and there is no data on the plasma adrenaline level needed to treat anaphylaxis. *neffy* demonstrated a pharmacokinetic profile that is within the range of approved injection products. The integrated pharmacokinetic parameters of adrenaline are summarised in Figure 3 (single dose) and Figure 4 (repeat dose) below.

Figure 3 Mean (SD) Single Dose Plasma Concentration vs Time Profiles of Adrenaline (linear scale)

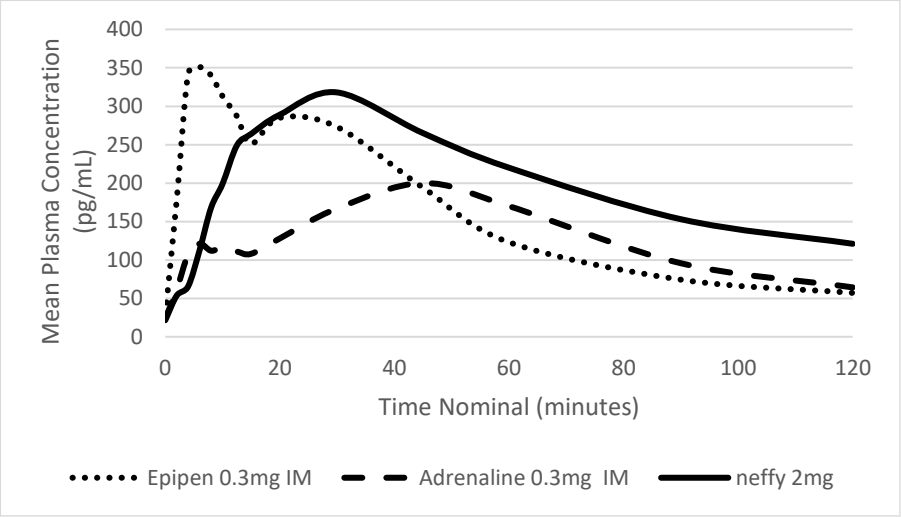
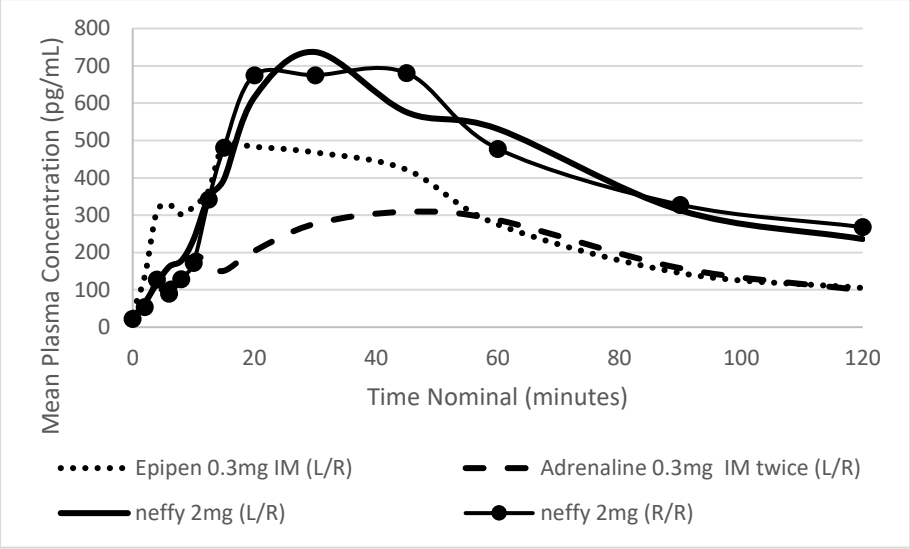


Figure 4 Mean (SD) Twice Dose Plasma Concentration vs Time Profiles of Adrenaline (linear scale)



Metabolism

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

Excretion

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

See Section 5.1 PHARMACODYNAMIC PROPERTIES for a description for Study EPI 10.

In paediatric patients with type I allergy without anaphylaxis who weigh 15 kg or greater (age range: 4 to 17 years), following one nasal dose of *neffy* 1 mg (for subjects who weigh 15 kg to < 30 kg) or 2 mg (for subjects who weigh 30 kg or greater), the geometric mean plasma epinephrine concentration time profiles for both weight groups were numerically higher than that of adults who received *neffy* 2 mg (Studies EPI 15 and 17).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Adrenaline and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay. Adrenaline had a moderate degree of mutagenicity and was positive in the DNA Repair test with *B. Subtilis* (REC) assay but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

Studies of adrenaline after repeated exposure in animals to evaluate the mutagenic potential have not been conducted. This should not prevent the use of adrenaline under the conditions noted under Section 4.1 THERAPEUTIC INDICATIONS.

Carcinogenicity

Studies of adrenaline after repeated exposure in animals to evaluate the carcinogenic potential have not been conducted. This should not prevent the use of adrenaline under the conditions noted under Section 4.1 THERAPEUTIC INDICATIONS.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride
Dodecyl-beta-D-maltoside
Disodium edetate
Benzalkonium chloride
Sodium metabisulphite
Hydrochloric acid

Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Patients should be advised to ensure neffy is stored below 25° C. However, short term accidental exposure to temperatures up to a maximum of 50° C are permitted.

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

Container type

neffy is filled into a Type I glass vial and closed with a bromobutyl rubber stopper. The vial is enclosed in a white polypropylene holder which forms part of the single-dose nasal spray.

Pack sizes

neffy is supplied in a carton containing two (2) blister packages each with a single-dose nasal spray for 1 time use.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

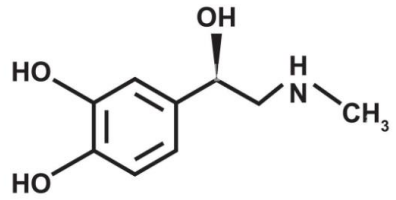
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical name: (R)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Structural formula:



Molecular formular: $C_9H_{13}NO_3$
Molecular weight: 183.2

CAS number

CAS registry number: 51-43-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4): Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

8th December 2025

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

neffy is a registered trademark of ARS Pharmaceuticals Operations, Inc.