Product Monograph Including Patient Medication Information

neffy®

epinephrine nasal spray

2 mg/0.1 mL dose

Catecholamine/Sympathomimetic

Date of Authorization:

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RECENT MAJOR LABEL CHANGES

NA	

Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1 Indications

neffy (epinephrine nasal spray) is indicated for:

- the emergency treatment of allergic reactions (anaphylaxis) due to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis in adult and pediatric patients who weigh 30 kg or greater.

1.1 Pediatrics

Pediatrics (<30 kg): Health Canada has not authorized an indication for patients <30 kg.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical experience suggests that the use of epinephrine in geriatric patients is associated with differences in safety. See 7.1.4 GERIATRICS.

2 Contraindications

There are no absolute contraindications to the use of epinephrine in a life-threatening allergic situation.

4 Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of **neffy** is one spray (2 mg of epinephrine) administered into one nostril. In the absence of clinical improvement or if symptoms worsen after the initial treatment, a second dose of **neffy** may be administered in the same nostril with a second nasal spray starting 5 minutes after the first dose.

- Advise patients when to seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event further treatment is required.
- It is recommended that patients are prescribed and have immediate access to two **neffy** nasal sprays at all times.

4.4 Administration

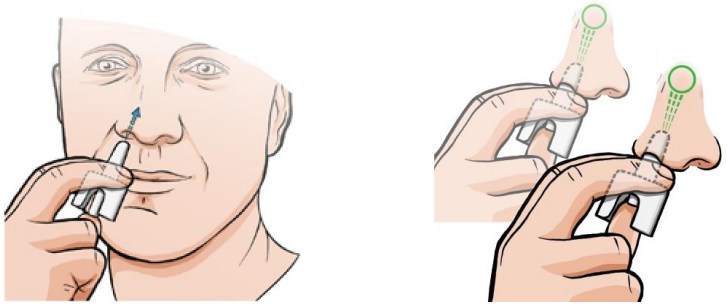
- **neffy** is for nasal use only.
- Each **neffy** nasal spray is for single use and delivers the entire dose upon activation.
- Do not prime or attempt to reuse **neffy** for more than one administration.
- Self-administration: Use the right hand to administer **neffy** to the right nostril and use the left hand to administer **neffy** to the left nostril.

- Care-giver administration: Use the right hand to administer **neffy** to the left nostril and use the left hand to administer **neffy** to the right nostril.

Administer **neffy** by inserting the nozzle of the nasal spray fully into one nostril (see Figure 1). Hold the nasal spray straight into the nose - do not angle the nasal spray to the inside septum or outer wall of the nose as some medication may be lost. Press the plunger firmly to activate. Avoid sniffing during and after administration. If a second dose of **neffy** is needed, administer a new nasal spray into the same nostril starting 5 minutes after the first dose. More than two sequential doses of epinephrine should be administered under direct medical supervision. Refer patients and caregivers to the *Instructions for Use* for detailed administration instructions.

Figure 1: Administration of neffy

First Dose **Second Dose in the Same Nostril**



If **neffy** is frozen and is needed in an emergency, do not wait to thaw, seek emergency medical care immediately.

5 Overdose

Symptoms

Overdose of epinephrine 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 epinephrine may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking medicinal products.

If an epinephrine 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.

Epinephrine 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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intranasal	Solution for intranasal administration, 2 mg/0.1 mL	Benzalkonium chloride, disodium edetate, n-dodecyl beta-D-maltoside, sodium chloride, sodium metabisulfite, and hydrochloric acid or sodium hydroxide to adjust pH, in water for injection

neffy is an aqueous solution packaged in Type I glass vials and closed with a grey bromobutyl rubber stopper and then assembled into a Unit Dose Sprayer device. The device is a non-pressurized dispenser delivering a single-dose nasal spray.

Pack size: Pack of 2 single-dose nasal sprays
Pack of 1 single-dose nasal spray

7 Warnings and Precautions

Emergency Treatment

neffy is intended for immediate administration as emergency supportive therapy and is not intended as a substitute for immediate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision. Advise patients when to seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event further treatment is required.

Patients should be instructed to recognise symptoms of systemic allergic reactions and anaphylaxis that may occur within minutes after allergen 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.

General

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). Absorption of **neffy** may be affected by underlying structural and anatomical nasal conditions. Consider use of other epinephrine products given by other routes of administration for patients with underlying structural or anatomical nasal conditions.

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer **neffy** to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

For information on the **neffy** Education Program (Training device, Training video, Patient education brochure and Instructions for use), please refer to the website (www.alk.net/ca/neffy-materials/) or scan the QR code on the package labels (carton and blister).

Cardiovascular

Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris, as well as produce ventricular arrhythmias (see 8 ADVERSE REACTIONS AND 9 DRUG INTERACTIONS).

Endocrine and Metabolism

Patients with diabetes may develop increased blood glucose levels following epinephrine administration.

Epinephrine can temporarily exacerbate the underlying condition or increase symptoms in patients with hyperthyroidism.

Neurologic

Epinephrine use should be avoided in patients with organic brain damage.

Patients with Parkinson's disease may notice a temporary worsening of symptoms after treatment with epinephrine.

Ophthalmologic

Epinephrine use should be avoided in patients with narrow-angle glaucoma.

In patients with high intraocular pressure in angle-closure glaucoma, epinephrine dilates the pupil (mydriasis) and produces an acute episode of angle-closure. Epinephrine reduces intraocular pressure in open-angle glaucoma, decreasing aqueous formation and increasing outflow facility.

Renal

Epinephrine can temporarily exacerbate the underlying condition or increase symptoms in patients with renal impairment. Epinephrine should be administered with caution in patients with these conditions, including elderly patients and pregnant women.

Reproductive Health: Female and Male Potential

There are no data on the effect of **neffy** on human fertility.

Sensitivity

Epinephrine 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 epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in **neffy** should not deter administration of the drug for treatment of serious allergic or other emergency situations.

7.1 Special Populations

7.1.1 Pregnant Women

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

Animal studies do not indicate reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY).

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

7.1.2 Breastfeeding

There are no data on the effect of epinephrine in breast-feeding women. However, **neffy** should be used in the same manner in breastfeeding and non-breastfeeding women.

It is unknown whether epinephrine/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.

7.1.3 Pediatrics (patients less than 30 kg)

The safety and efficacy of **neffy** in pediatric patients weighing less than 30 kg have not been established; therefore, Health Canada has not authorized an indication for pediatric use in this weight group.

7.1.4 Geriatrics

Clinical pharmacology studies of **neffy** for the emergency treatment of type I allergic reactions, including anaphylaxis, did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger adult subjects. However, other reported clinical experience with use of epinephrine for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of epinephrine (see 5 OVERDOSE AND 7 WARNINGS AND PRECAUTIONS). **neffy** should be administered with caution in elderly patients who are at greater risk for developing adverse reactions after epinephrine administration.

8 Adverse Reactions

8.1 Adverse Reaction Overview

The most frequently occurring adverse reactions (very common events ≥ 10%) observed in clinical studies of **neffy** were reported only after a 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect the frequencies observed in clinical practice and should not be compared to the frequencies reported in clinical trials of another drug.

The safety of **neffy** 2 mg is primarily based on four clinical pharmacology studies in 175 healthy adults and adults with type I allergy without anaphylaxis, who did not have structural or anatomical nasal conditions (see 10 CLINICAL PHARMACOLOGY). The four clinical pharmacology studies were designed to compare the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of one dose of **neffy** 2 mg sprayed into one nostril or two doses of **neffy** 2 mg sprayed into either the same or opposite nostril, administered 10 minutes apart, with PK and PD profiles of one or two dose(s) of epinephrine injection administered intramuscularly. The common adverse reactions that occurred with **neffy** 2 mg after one and two dose(s) are listed in Table 2.

Table 2: Adverse Reactions with One or Two Dose(s) of neffy with Incidence Greater than or Equal to 2% in Adults [Studies EPI 15, EPI 16, EPI 17, and EPI 18]

Adverse Reaction**	neffy 2 mg One Dose n = 134***		neffy 2 mg Two Doses* n = 85***	
	n	%	n	%
Gastrointestinal disorders				
Abdominal pain	1	1%	3	4%
Gingival pain	0	0%	3	4%
Hypoesthesia Oral	0	0%	3	4%
Nausea	4	3%	2	2%
Vomiting	3	2%	2	2%
General disorders and administration site conditions				
Feeling jittery	1	1%	9	11%
Nervous system disorders				
Dizziness	4	3%	2	2%
Headache	8	6%	15	18%
Tremor	0	0%	7	8%

Adverse Reaction**	neffy 2 mg One Dose n = 134***		neffy 2 mg Two Doses* n = 85***	
	n	%	n	%
Respiratory, thoracic and mediastinal disorders				
Nasal congestion	0	0%	2	2%
Nasal discomfort	13	10%	11	13%
Nasal pruritus	0	0%	3	4%
Rhinorrhoea	4	3%	6	7%
Sneezing	0	0%	3	4%
Throat irritation	2	2%	16	19%

* Two nasal doses of **neffy** 2 mg were administered 10 minutes apart
** Data include subjects with nasal allergen challenge induced rhinitis
*** The trials used a crossover design and therefore the total number of subjects do not match the number of unique subjects (n = 175)

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

A single-arm PK/PD study (EPI 10) in pediatric subjects 8 to 17 years of age who weigh 30 kg or greater with type I allergy without anaphylaxis was conducted to assess the PK/PD of **neffy** 2 mg. A total of 42 pediatric subjects who weigh 30 kg or greater (body weight range: 31 kg to 95 kg; age range: 8 to 17 years) were enrolled, including 21 subjects who received one nasal dose of **neffy** 2 mg . Common adverse reactions reported in these subjects who received one dose of **neffy** 2 mg include nasal discomfort (19%), intranasal paresthesia (19%), rhinorrhea (19%), sneezing (14%), paresthesia (10%), fatigue (10%), and feeling jittery (10%).

There were no clinically relevant differences in the safety between the pediatric and adult populations treated with **neffy** 2 mg.

8.3 Less Common Clinical Trial Adverse Reactions

Ear and labyrinth disorders: ear pain

Eye disorders: blepharospasm, eye irritation, lacrimation increased, ocular discomfort

Gastrointestinal: diarrhea, gingival discomfort, odynophagia, oral discomfort, salivary hypersecretion, toothache

General disorders and administration site conditions: chills, feeling cold, feeling hot, mucosal disorder, pyrexia, secretion discharge

Investigations: body temperature decreased, body temperature increased, heart rate decreased

Musculoskeletal and connective tissue disorders: temporomandibular joint syndrome, muscle spasms

Nervous system disorders: presyncope, somnolence, syncope

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dry throat, oropharyngeal pain, Increased upper airway secretion, pharyngeal hypoesthesia, pharyngeal paraesthesia, rhinalgia

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, skin discoloration, skin lesions

Vascular disorders: hypotension, hot flush

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Eye disorders: lacrimation increased

Respiratory, thoracic and mediastinal disorders: epistaxis, nervousness, oropharyngeal pain, pharyngeal paraesthesia

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during use of epinephrine. 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 hemorrhage, hypertension, pallor, palpitations, tachyarrhythmia, tachycardia, vasoconstriction, ventricular ectopy, and stress cardiomyopathy

Metabolism and nutrition disorders: transient hyperglycemia, sweating

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

Psychiatric disorders: apprehensiveness, restlessness

Respiratory disorders: respiratory difficulties

9 Drug Interactions

9.2 Drug Interactions Overview

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.

9.3 Drug-Behavioural Interactions

Tell your doctor if you are drinking alcohol because this can increase the effects of epinephrine.

9.4 Drug-Drug Interactions

The effects of epinephrine 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, tropicamide), certain antihistamines (diphenhydramine, chlorpheniramine), levodopa, and alcohol.

Pressor effects of epinephrine:

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

Epinephrine and insulin:

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

Epinephrine and beta-blocking medicinal products:

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Epinephrine 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.

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

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

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

10.2 Pharmacodynamics

Four clinical pharmacology studies of **neffy** in adults and one clinical pharmacology study in pediatric subjects who weigh 30 kg or greater are described below.

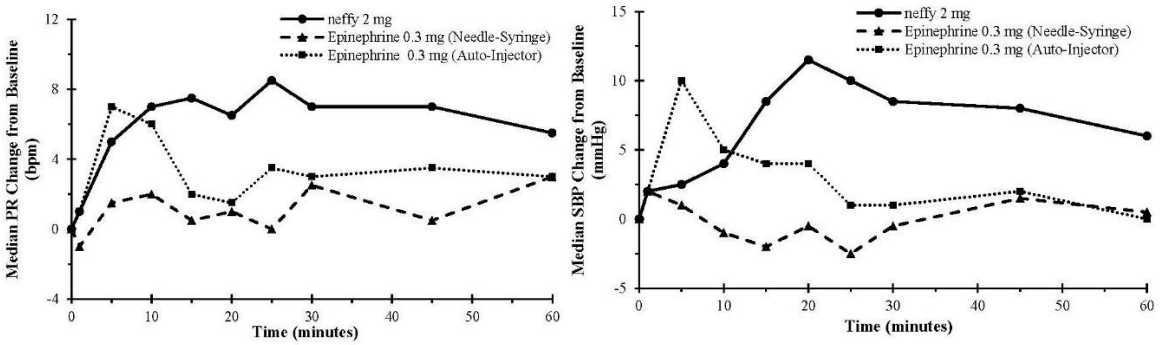
Systolic blood pressure and pulse rate in healthy adult subjects (Study EPI 15):

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

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

Results following one dose of all epinephrine products demonstrated an increase from baseline SBP and PR as shown in Figure 2.

Figure 2: Median pulse rate (PR) and systolic blood pressure (SBP) change from baseline following one dose of epinephrine in healthy subjects [Study EPI 15]



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

Systolic blood pressure and pulse rate in adult patients with Type I allergy without anaphylaxis (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 epinephrine following self-administered one nasal dose of **neffy** 2 mg to staff-administered one intramuscular dose of epinephrine 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 Study EPI 15.

Systolic blood pressure and pulse rate 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 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.

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

- One nasal dose of **neffy** 2 mg without nasal allergen challenge (NAC).
- One nasal dose of **neffy** 2 mg after undergoing NAC to induce rhinitis/nasal congestion.
- One intramuscular dose of epinephrine injection 0.3 mg (using a needle syringe) without NAC.
- One intramuscular dose of epinephrine injection 0.5 mg (using a needle syringe) without NAC.

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

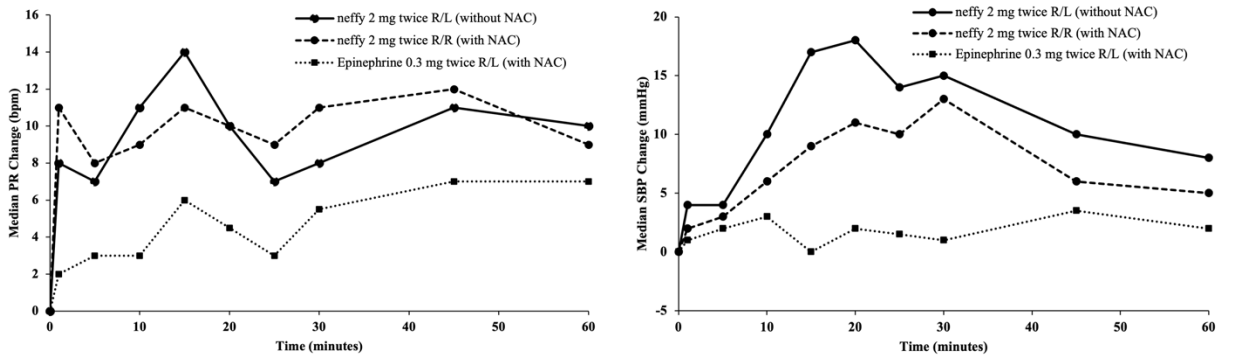
- Median SBP and PR for **neffy** with NAC initially increased from baseline, but the median responses were lower than the use of **neffy** without NAC after 5 to 15 minutes post-dose.
- Median SBP response for **neffy** with NAC was initially higher than the median SBP response for the intramuscular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

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

- Two nasal doses of **neffy** 2 mg (in the opposite nares (right(R)/left (L)) without NAC.
- Two intramuscular (IM) doses of epinephrine injections 0.3 mg (using a needle-syringe; in the opposite thigh (R/L)) without NAC.
- Two nasal doses of **neffy** 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 epinephrine injections 0.3 mg (using a needle-syringe; 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 3: Median change from baseline for systolic blood pressure (SBP) and pulse rate (PR) following two doses of epinephrine 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]



R/L: First dose administered in right naris followed by second dose administered in left naris 10 minutes apart.

R/R: First dose administered in right naris followed by second dose administered in right naris 10 minutes apart.

Epinephrine 0.3 mg was administered using needle-syringe product

Pediatric population:

Systolic blood pressure and pulse rate in pediatric patients with type I allergy without anaphylaxis (Study EPI 10)

Study EPI 10 was a single-arm study conducted in pediatric patients who weighed 30 kg or greater (age range: 8 to 17 years) with type I allergy without anaphylaxis (N=21) that assessed the PK and PD of epinephrine following one nasal dose of **neffy** 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 **neffy** in Study EPI 15.

10.3 Pharmacokinetics

Absorption

Following one nasal dose of **neffy** 2 mg, the geometric mean plasma epinephrine concentration-time profile was overall within the range of that following one intramuscular dose of epinephrine injection 0.3 mg (using a needle-syringe product and an auto-injector product) 60 minutes post-dose. The integrated pharmacokinetic parameters of epinephrine are summarized in Table 3**.**

Table 3: Mean (CV%) and geometric mean plasma PK parameters following one or two doses of epinephrine (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
neffy 2 mg IN (HCP administration)	78	20.5 (2 - 150)	485 (70.6)	361	40900 (67.5)	32600
neffy 2 mg IN (self-administration)	32	30 (10 - 240)	448 (67.1)	342	50365 (55.5)	41077
neffy 2 mg IN (pediatrics)	16	25.0 (2.5 - 120)	540 (70.7)	433	35500 (76.3)	27800
neffy 2 mg twice (L/R)	39	30 (6 - 150)	1000 (93.1)	706	86000 (77)	66700
neffy 2 mg twice (R/R)	39	30 (4 - 150)	992 (75.3)	729	86500 (60.5)	69900
Epinephrine 0.3 mg IM	178	45 (3.9 -360)	277 (65.4)	234	27900 (38.7)	26100
Epinephrine 0.3 mg IM twice	70	45 (6 - 180)	436 (48.8)	386	47500 (32.6)	45300
Epinephrine auto-injector 0.3 mg	77	10 (2 - 45)	581 (75.6)	447	31600 (39.3)	29200
Epinephrine auto-injector 0.3 mg twice	78	20 (4 - 360)	754 (64.7)	630	55000 (47.9)	29200

IN: intranasal; IM: intramuscular

Epinephrine has a rapid onset of action after administration. Following nasal administration to healthy volunteers, epinephrine 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), epinephrine is absorbed more rapidly with the maximum concentration observed in about 10 minutes.

Biotransformation

Epinephrine 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 epinephrine is excreted as metabolites in urine. Elimination is mainly via metabolism of the liver and kidneys, with a small amount excreted unchanged in the urine. The plasma half-life following nasal administration is about 2 to 3 minutes.

Special Populations and Conditions

Pediatric patients with type I allergies without anaphylaxis (Study EPI 10)

In pediatric patients with Type I allergies weighing 30 kg or greater (age range: 8 to 17 years), following a single 2 mg nasal dose of **neffy**, the geometric mean plasma epinephrine 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 3).

11 Storage, Stability, and Disposal

Store at 15°C to 30°C for up to 30 months. Excursions permitted up to 50°C.

Do not freeze. **neffy** freezes below -15°C. If **neffy** freezes, it will not deliver epinephrine.

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

Part 2: Scientific Information

13 Pharmaceutical Information

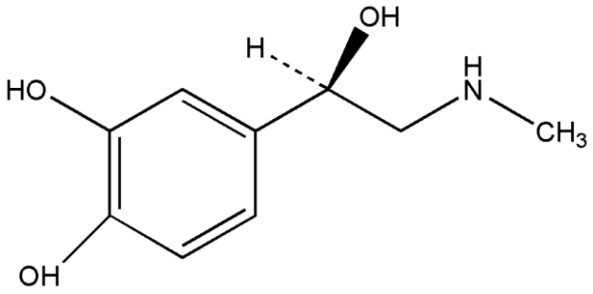
Drug Substance

Proper name: Epinephrine

Chemical name: (-)-3,4-dihydroxy-α-[(methylamino)methyl] benzyl alcohol

Molecular formula and molecular mass: C9H13N03 and 183.21 g/mol

Structural formula:



Physicochemical properties: Epinephrine is a white to practically white, odorless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Its solutions are alkaline to litmus.

Product Characteristics

General properties of epinephrine are outlined below:

Appearance (color, physical form)	White to almost white crystalline powder
Solubility	Soluble in aqueous solutions of mineral acids. Very slightly soluble in ethanol and methanol. Practically insoluble in acetone, chloroform, methylene chloride, and ether.
Melting range	215°C
Solution pH	The pH of an aqueous solution is slightly alkaline
Specific Rotation	− 50° to − 54°

14 Clinical Trials

Controlled clinical trials for treatment of the indicated condition (anaphylaxis) have not been performed with epinephrine. See 10 CLINICAL PHARMACOLOGY for clinical trial information related to the pharmacokinetics and pharmacodynamic effects of **neffy**.

16 Non-clinical Toxicology

General Toxicology

In a single-dose nasal toxicity study, treatment of epinephrine nasal spray solution in rats induced epinephrine-related histopathology changes in the nose, such as minimal ulceration of the exposed mucosa (at ≥2.3-fold the recommended clinical dose of **neffy** 2 mg based on local surface area), and nasal passages, such as minimal to mild necrosis in the nasal turbinate and parietal wall in the rostral-most level (at ≥1.2-fold the recommended clinical dose of **neffy** 2 mg based on local surface area) on day 2. These findings were often associated with minimal to mild neutrophilic inflammation and were reversible after 14 days post-dose.

Carcinogenicity

Long-term studies to evaluate the carcinogenic potential of epinephrine have not been conducted.

Genotoxicity

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This should not prevent the use of epinephrine where indicated (see 1 INDICATIONS).

Reproductive Toxicity

In an embryofetal development study with pregnant rabbits dosed during the period of organogenesis (on days 3 to 5, 6 to 7 or 7 to 9 of gestation), epinephrine caused teratogenic effects (including gastroschisis) at doses approximately 15 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1.2 mg/kg/day for two to three days). Animals treated on days 6 to 7 had decreased number of implantations.

In an embryofetal development study, pregnant mice were administered epinephrine (0.1 to 10 mg/kg/day) on Gestation Days 6 to 15. Teratogenic effects, embryonic lethality, and delays in skeletal ossification were observed at approximately 3 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

In an embryofetal development study with pregnant hamsters dosed during the period of organogenesis from gestation days 7 to 10, epinephrine produced reductions in litter size and delayed skeletal ossification at doses approximately 2 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m^2 basis at a maternal subcutaneousdose of 0.5 mg/kg/day).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

neffy

epinephrine nasal spray

This Patient Medication Information is written for the person who will be taking **neffy**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **neffy**, talk to a healthcare professional.

What neffy is used for:

- neffy is used in adults and children with a body weight of 30 kg (66 pounds) or more for the emergency treatment of allergic reactions, including anaphylaxis to insect stings or bites, foods, medicines and other allergens, as well as anaphylaxis where the cause is not known or anaphylaxis caused by exercise.

- neffy is intended for immediate self (or caregiver) administration in an allergic emergency.

Symptoms of anaphylaxis may include:

- Raised rash (like a nettle rash) or itching of skin
- Shortness of breath, wheezing
- Fast heartbeat
- Loss of bladder control
- Nausea, vomiting, diarrhea or stomach cramps
- Swelling of the lips, throat, tongue, hands or feet
- Hoarseness
- Flushing
- Apprehension or fitting

How neffy works:

neffy contains epinephrine. When sprayed in the nostril, it works directly on the heart and lung systems to stop the possible fatal effects of a severe allergic reaction that can lead to anaphylactic shock. It improves blood pressure, heart function and breathing, and reduces tissue swelling.

The ingredients in neffy are:

Medicinal ingredients: Epinephrine

Non-medicinal ingredients: Benzalkonium chloride, disodium edetate, -dodecyl beta-D-maltoside, sodium chloride, sodium metabisulfite, and hydrochloric acid or sodium hydroxide to adjust pH, in water for injection.

neffy comes in the following dosage forms:

Nasal spray solution; each dose delivers 2 mg of epinephrine in 0.1 mL of solution.

Do not use neffy if:

- There is no known reason why anyone should not use neffy during an allergic emergency.

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

- Are allergic to any of the ingredients in neffy
- Have or have a history of nasal problems such as polyps, nasal fractures or injuries, or nasal surgery
- Have heart disease
- Have an irregular heart beat (arrythmia)
- Have coronary artery disease
- Have high blood pressure
- Have diabetes
- Have an overactive thyroid gland (hyperthyroidism)
- Have any brain damage
- Have Parkinson's disease
- Have narrow-angle glaucoma
- Have kidney problems
- Are 65 years of age or older
- Are pregnant, or think you may be pregnant
- Are breastfeeding

Other warnings you should know about:

General: Always carry neffy with you because you may not know when anaphylaxis may happen. It is recommended that you carry at least two neffy nasal sprays in case you need a second dose. After using neffy, get emergency medical help for further treatment of the allergic emergency (anaphylaxis).

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

The following may interact with neffy:

- Medicines that make the heart sensitive to arrythmias (irregular heart beat) such as digoxin, mercurial diuretics (medicines that increase urine production such as chlormerodrin, merbaphen, mersalyl acid, meralluride, mercaptomerin, mercurophylline, merethoxylline procaine) or quinidine
- Antidepressants called 'tricyclic antidepressants' such as imipramine
- Antidepressants called 'monoamine oxidase inhibitors' such as isocarboxazid, phenelzine, selegiline, tranylcypromine
- Medicines used to treat Parkinson's disease such as entacapone, tolcapone, carbidopa-levodopa-entacapone, opicapone, levodopa

- Medicines used in the treatment of thyroid disease such as levothyroxine
- Medicines called ‘parasympatholytics’, which affect the nervous system (such as atropine, cyclopentolate, homatropine, hyoscine, tropicamide)
- Medicines used to treat high blood pressure
- Medicines called ‘beta-blockers’, which are used to lower blood pressure (such as propranolol)
- Medicines called ‘alpha-adrenergic blockers’, which relax smooth muscles in the body (such as phentolamine)
- Medicines used to treat allergies such as diphenhydramine, chlorpheniramine
- Theophylline, often used to treat asthma or chronic obstructive pulmonary disease (COPD)
- Oxytocin, used during labour
- Insulin, used in the treatment of diabetes
- Alcohol

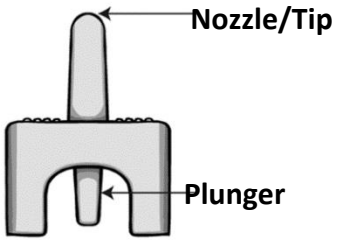
How to take neffy:

- Read the Instructions for Use before you use neffy.
- Always use neffy exactly as your healthcare professional has told you.
- neffy is for use in the nose only.
- Each bottle is single-use. Do NOT test the spray bottle or try to reuse it, the bottle contains only one dose.
- For information on the neffy Education Program (training device, training video, patient education brochure and Instructions for Use), go to www.alk.net/ca/neffy-materials, or scan the QR code on the package labels.
- If you have any questions about neffy, ask your healthcare professional.

Instructions for use

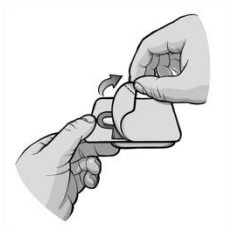
Before you need to use it, fully familiarise yourself with neffy, including when and how it should be used.

neffy 2 mg nasal spray:



Follow these instructions only when ready to use.

A



Remove neffy 2 mg nasal spray from packaging.
Pull open the packaging to remove the neffy 2 mg nasal spray.

B

Hold the nasal spray as shown.
Hold the nasal spray with your thumb on the bottom of the plunger and one finger on either side of the nozzle.

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

C

Insert tip of nasal spray into a nostril .

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.

D

Press plunger up firmly until it snaps up and sprays into the nostril.

Avoid sniffing during and after administration. If any liquid drips out of the nose, monitor for symptoms. You may need to give a second dose of neffy.

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

Seek emergency medical assistance
Get emergency medical help for further treatment of the allergic emergency (anaphylaxis) after using neffy.

Monitor patient symptoms
If symptoms continue to worsen or reoccur after approximately 5 minutes, or if there was any error in administration, use a new neffy nasal spray, to give a second dose in the SAME nostril as the first dose and seek urgent emergency medical assistance.

If necessary, you can lie down with feet raised. If this makes you breathless, you should sit up. Unconscious patients should be placed on their side in the recovery position to prevent choking. If symptoms do not resolve, you should, if possible, remain with another person until medical assistance arrives.

If you use more neffy than you should

In case of an overdose of the epinephrine, you should always seek immediate medical help.

Overdose may cause a sudden increase in blood pressure (with symptoms including headache or dizziness), bleeding in brain tissue, palpitations (forceful heartbeats that may be rapid or irregular), reduced blood flow and accumulation of fluid in the lungs (causing symptoms including difficulty breathing). You will need to be monitored.

If you have any further questions on the use of this medicine, ask your healthcare professional.

Usual dose:

The usual dose is one spray (2 mg of epinephrine) into one nostril. If the symptoms do not improve after approximately 5 minutes, use a new neffy nasal spray to deliver a second dose into the **SAME** nostril. The maximum dose is two sprays (4 mg of epinephrine).

It is recommended that you have at least two neffy nasal sprays on hand.

Overdose:

If you think you, or a person you are caring for, have taken too much neffy, contact a healthcare professional, hospital emergency department, regional poison control centre, or Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using neffy:

These are not all the possible side effects you may have when taking neffy. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of neffy may include:

- throat irritation
- tingling nose
- headache
- nasal discomfort
- feeling overly excited, nervous, or anxious
- tingling sensation
- fatigue
- shakiness
- runny nose
- itchy nose
- sneezing
- stomach pain
- pain in the gums or teeth
- numbness in the mouth
- nasal congestion
- dizziness
- nausea
- vomiting

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Angina (chest pain): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest			X
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat			X
Difficulty breathing			X

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

Reporting side effects

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

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store at 15°C to 30°C. Do not freeze.

If accidentally frozen, the nasal spray device will not work. Allow the nasal spray to thaw for at least one hour. Do not use if the contents are still frozen or not completely thawed.

Keep this medicine out of sight and reach of children who are not the intended user.

If you want more information about neffy:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the company's website: www.alk.net/ca or by calling (1-800-663-0972).

This information is current up to the time of the last authorization date shown below, but more current information may be available from the manufacturer.

This leaflet was prepared by ALK-Abelló A/S.

Date of Authorization: 2026-04-09