

## **AVAMYS NASAL SPRAY**

### **Fluticasone furoate**

## **QUALITATIVE AND QUANTITATIVE COMPOSITION**

AVAMYS Nasal Spray is a white, uniform suspension contained in an amber glass bottle, fitted with a metering (50 microlitres) atomising spray pump. This inner pack is incorporated within a predominantly off-white plastic device with a blue side-actuated lever and a lid which contains a stopper. Each spray of the suspension delivers approximately 27.5 micrograms of micronised fluticasone furoate as an ex-device dose.

## **PHARMACEUTICAL FORM**

Nasal spray, suspension.

## **CLINICAL PARTICULARS**

### **Indications**

#### **Adults and Adolescents (12 years and older)**

Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) and ocular symptoms (itching/burning, tearing/watering, and redness of the eye) of seasonal allergic rhinitis.

Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) of perennial allergic rhinitis.

#### **Children (2 to 11 years)**

Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) of seasonal and perennial allergic rhinitis.

### **Dosage and Administration**

AVAMYS Nasal Spray is for administration by the intranasal route only. For full therapeutic benefit, regular scheduled usage is recommended. Onset of action has been observed as early as 8 hours after initial administration. It may take several days of treatment to achieve maximum benefit. An absence of an immediate effect should be explained to the patient (*see Clinical Studies*).

### **Populations**

For the treatment of seasonal allergic rhinitis and perennial allergic rhinitis:

### **Adults and Adolescents (12 years and older)**

The recommended starting dosage is 2 sprays (27.5 micrograms per spray) in each nostril once daily (total daily dose, 110 micrograms).

Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril once daily (total daily dose, 55 micrograms) may be effective for maintenance.

### **Children (2 to 11 years)**

The recommended starting dosage is 1 spray (27.5 micrograms per spray) in each nostril once daily (total daily dose, 55 micrograms).

Patients not adequately responding to 1 spray in each nostril once daily (total daily dose, 55 micrograms) may use 2 sprays in each nostril once daily (total daily dose, 110 micrograms). Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril once daily (total daily dose, 55 micrograms) is recommended.

### **Children (under 2 years of age)**

There are no data to recommend use of AVAMYS Nasal Spray for the treatment of seasonal or perennial allergic rhinitis in children under 2 years of age.

### **Elderly**

No dosage adjustment required (*see Pharmacokinetics*).

### **Renal impairment**

No dosage adjustment required (*see Pharmacokinetics*).

### **Hepatic impairment**

No dosage adjustment is required in patients with hepatic impairment (*see Warnings and Precautions, and Pharmacokinetics*).

### **Contraindications**

AVAMYS Nasal Spray is contra-indicated in patients with hypersensitivity to any of the ingredients.

### **Warnings and Precautions**

Based on data with another glucocorticoid metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate (*see Interactions and Pharmacokinetics*).

Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different

corticosteroid preparations. A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 micrograms daily for one year (*see Adverse Reactions and Clinical Studies*). Therefore, children should be maintained on the lowest dose which delivers adequate symptom control (*see Dosage and Administration*). As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes such as central serous chorioretinopathy (*see Clinical Studies*).

## **Interactions**

Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the cytochrome P450 3A4. In a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole, there were more subjects with measurable fluticasone furoate plasma concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 of the 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups.

The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between fluticasone furoate and the cytochrome P450 mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of fluticasone furoate on other drugs (*see Warnings and Precautions, and Pharmacokinetics*).

## **Pregnancy and Lactation**

Adequate data are not available regarding the use of AVAMYS Nasal Spray during pregnancy and lactation in humans. AVAMYS Nasal Spray should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus.

### **Fertility**

There are no data in humans (*see Pre-Clinical Safety Data, Reproductive Toxicology*).

### **Pregnancy**

Following intranasal administration of AVAMYS Nasal Spray at the maximum recommended human dose (110 micrograms/day), plasma fluticasone furoate concentrations were typically non-quantifiable and therefore potential for reproductive toxicity is expected to be very low (*see Pre-Clinical Safety Data , Reproductive Toxicology*).

### **Lactation**

The excretion of fluticasone furoate into human breast milk has not been investigated.

## Effects on Ability to Drive and Use Machines

Based on the pharmacology of fluticasone furoate and other intranasally administered steroids, there is no reason to expect an effect on ability to drive or to operate machinery with AVAMYS Nasal Spray.

## Adverse Reactions

Data from large clinical trials were used to determine the frequency of adverse reactions. The following convention has been used for the classification of frequency: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

### Clinical Trial Data

#### Respiratory, thoracic and mediastinal disorders

Very common:	Epistaxis
In adults and adolescents, the incidence of epistaxis was higher in longer-term use (more than 6 weeks) than in short-term use (up to 6 weeks). In paediatric clinical studies of up to 12 weeks duration the incidence of epistaxis was similar between AVAMYS Nasal Spray and placebo.	
Common:	Nasal ulceration

### Children

#### Musculoskeletal and connective tissue disorders

Not known:	Growth retardation
In a one-year clinical study assessing growth in pre-pubescent children receiving 110 micrograms of fluticasone furoate once daily, an average treatment difference of -0.27 cm per year in growth velocity was observed compared to placebo (see Clinical Studies).	

### Post-Marketing Data

#### Immune system disorders

Rare:	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria
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## Nervous system disorders

Common:	Headache.
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## Respiratory, thoracic and mediastinal disorders

Uncommon:	Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness.
Very rare:	Nasal septum perforation

## Overdose

### Symptoms and Signs

In a bioavailability study, intranasal doses of up to 24 times the recommended daily adult dose were studied over three days with no adverse systemic effects observed (*see Pharmacokinetics*).

### Treatment

Acute overdose is unlikely to require any therapy other than observation.

## PHARMACOLOGICAL PROPERTIES

### Mechanism of Action

Fluticasone furoate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action.

### Pharmacokinetics

#### *Absorption*

Fluticasone furoate undergoes extensive first-pass metabolism and incomplete absorption in the liver and gut resulting in negligible systemic exposure. The intranasal dosing of 110 micrograms once daily does not typically result in measurable plasma concentrations (less than 10 picograms/mL). The absolute bioavailability for fluticasone furoate administered as 880 micrograms three times per day (2640 micrograms total daily dose) is 0.50%.

### ***Distribution***

The plasma protein binding of fluticasone furoate is greater than 99%. Fluticasone furoate is widely distributed with volume of distribution at steady-state of, on average, 608 L.

### ***Metabolism***

Fluticasone furoate is rapidly cleared (total plasma clearance of 58.7L/h) from systemic circulation principally by hepatic metabolism to an inactive 17 beta-carboxylic metabolite (GW694301X), by the cytochrome P450 enzyme CYP3A4. The principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate function to form the 17 beta-carboxylic acid metabolite. *In vivo* studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone.

### ***Elimination***

Elimination was primarily via the faecal route following oral and intravenous administration indicative of excretion of fluticasone furoate and its metabolites via the bile. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Urinary excretion accounted for approximately 1% and 2 % of the orally and intravenously administered dose, respectively.

### ***Special Patient Populations***

#### **Elderly**

Only a small number of elderly subjects (n=23/872; 2.6%) provided pharmacokinetic data. There was no evidence for a higher incidence of subjects with quantifiable fluticasone furoate concentrations in the elderly, when compared to the younger subjects.

#### **Children**

Fluticasone furoate is typically not quantifiable (less than 10 picograms/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were observed in less than 16% of paediatric patients following intranasal dosing of 110 micrograms once daily and only less than 7% of paediatric patients following 55 micrograms once daily. There was no evidence for a higher incidence of quantifiable levels of fluticasone furoate in younger children (less than 6 years of age).

#### **Renal impairment**

Fluticasone furoate is not detectable in urine from healthy volunteers after intranasal dosing. Less than 1% of dose-related material is excreted in urine and therefore renal impairment would not be expected to affect the pharmacokinetics of fluticasone furoate.

#### **Hepatic impairment**

There are no data on intranasal fluticasone furoate in subjects with hepatic impairment. Data are available following inhaled administration of fluticasone furoate (as fluticasone furoate or fluticasone furoate/vilanterol) to subjects with hepatic impairment that are also

applicable for intranasal dosing. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment (Child-Pugh B) resulted in increased  $C_{max}$  (42%) and  $AUC(0-\infty)$  (172%) compared to healthy subjects. Following repeat dosing of orally inhaled fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (on average two-fold as measured by  $AUC(0-24)$ ) in subjects with moderate or severe hepatic impairment (Child-Pugh B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (fluticasone furoate/vilanterol 200/25 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. There was no effect on serum cortisol in subjects with severe hepatic impairment (fluticasone furoate/vilanterol 100/12.5 micrograms). Based on these findings the average predicted exposure for 110 micrograms of intranasal fluticasone furoate in patients population would not be expected to result in suppression of cortisol.

### Other pharmacokinetic

Fluticasone furoate is typically not quantifiable (less than 10 picograms/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were only observed in less than 31% of patients aged 12 years and above and in less than 16% of paediatric patients following intranasal dosing of 110 micrograms once daily. There was no evidence for gender, age (including paediatrics), or race to be related to those subjects with quantifiable levels, when compared to those without.

## Clinical Studies

### Adult and Adolescent Seasonal Allergic Rhinitis

Once daily 110 micrograms AVAMYS Nasal Spray resulted in a significant improvement in daily reflective (how patient felt over the preceding 12 hours) and instantaneous (how patient felt at the time of assessment) pre-dose total nasal symptom scores (rTNSS and iTNSS, comprising rhinorrhea, nasal congestion, sneezing and nasal itching) and daily reflective and instantaneous total ocular symptom scores (rTOSS, comprising itching/burning, tearing/watering and redness of the eyes) versus placebo (see table below). The improvement in nasal and ocular symptoms was maintained over the full 24 hours after once daily administration.

<b>Seasonal Allergic Rhinitis: Primary and secondary key endpoints</b>				
<b>Study</b>	<b>Primary Endpoint: Daily rTNSS</b>		<b>Secondary Endpoint: Daily rTOSS</b>	
	<b>LS Mean Difference</b>	<b>P-value (95% CI)</b>	<b>LS Mean Difference</b>	<b>P-value (95% CI)</b>
FFR20001	-2.012	<0.001 (-2.58, -1.44)	-	-
FFR30003	-0.777	0.003 (-1.28, -0.27)	-0.546	0.008 (-0.95, -0.14)

FFR103184	-1.757	<0.001 (-2.28, -1.23)	-0.741	<0.001 (-1.14, -0.34)
FFR104861	-1.473	<0.001 (-2.01, -0.94)	-0.600	0.004 (-1.01, -0.19)
rTNSS = reflective total nasal symptom scores; rTOSS = reflective total ocular symptom scores; LS = Least square; LS Mean Difference = LS mean change from baseline in active – LS mean change from baseline in placebo; CI = Confidence interval				

The distribution of the patients' perception of overall response to therapy (using a 7-point scale ranging from significantly improved to significantly worse) favoured AVAMYS Nasal Spray 110 micrograms over placebo, with a statistically significant treatment difference. Onset of action was experienced as early as eight hours after initial administration in two studies. Significant improvement in symptoms was observed in the first 24 hours in all four studies, and continued to improve over several days. The patients' quality of life (as assessed by the Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ), was significantly improved from baseline with AVAMYS Nasal Spray compared to placebo (Minimum Important Difference in all studies = improvement of at least -0.5 over placebo; treatment difference -0.690,  $p < 0.001$ , 95% CI -0.84, -0.54).

#### **Adult and Adolescent Perennial Allergic Rhinitis:-**

AVAMYS Nasal Spray 110 micrograms once daily resulted in a significant improvement in daily rTNSS (LS mean difference = -0.706,  $P = 0.005$ , 95% CI -1.20, -0.21). The improvement in nasal symptoms was maintained over the full 24 hours after once daily administration. The distribution of patients' perception of overall response to therapy was also significantly improved compared to placebo.

In a two-year study designed to assess the ocular safety of fluticasone furoate (110 micrograms once daily intranasal spray), adults and adolescents with perennial allergic rhinitis received either fluticasone furoate ( $n = 367$ ) or placebo ( $n = 181$ ). The primary outcomes [time to increase in posterior subcapsular opacity ( $\geq 0.3$  from baseline in Lens Opacities Classification System, Version III (LOCS III grade)) and time to increase in intraocular pressure (IOP;  $\geq 7$  mmHg from baseline)] were not statistically significant between the two groups. Increases in posterior subcapsular opacity ( $\geq 0.3$  from baseline) were more frequent in subjects treated with fluticasone furoate 110 micrograms [14 (4%)] versus placebo [4 (2%)] and were transient in nature for ten subjects in the fluticasone furoate group and two subjects in the placebo group. Increases in IOP ( $\geq 7$  mmHg from baseline) were more frequent in subjects treated with fluticasone furoate 110 micrograms: 7 (2%) for fluticasone furoate 110 micrograms once daily and 1 (<1%) for placebo. These events were transient in nature for six subjects in the fluticasone furoate group and one placebo subject. At weeks 52 and 104, 95% of subjects in both treatment groups had posterior subcapsular opacity values within  $\pm 0.1$  of baseline values



for each eye and, at week 104,  $\leq 1\%$  of subjects in both treatment groups had  $\geq 0.3$  increase from baseline in posterior subcapsular opacity. At weeks 52 and 104, the majority of subjects ( $>95\%$ ) had IOP values of within  $\pm 5\text{mmHg}$  of the baseline value. Increases in posterior subcapsular opacity or IOP were not accompanied by any adverse events of cataracts or glaucoma.

## **Children**

The paediatric posology is based on assessment of the efficacy data across the allergic rhinitis population in children. In a seasonal allergic rhinitis study in children, AVAMYS Nasal Spray 110 micrograms over two weeks was effective on primary (daily rTNSS LS mean difference =  $-0.616$ ,  $P=0.025$ , 95% CI  $-1.15$ ,  $-0.08$ ) and all secondary nasal endpoints, except the individual reflective score for rhinorrhea. No significant differences were observed between 55 micrograms AVAMYS Nasal Spray and placebo on any endpoint.

In a perennial allergic rhinitis study, AVAMYS Nasal Spray 55 micrograms was effective on daily rTNSS (LS mean difference =  $-0.754$ ,  $P=0.003$ , 95% CI  $-1.24$ ,  $-0.27$ ). Although there was a trend towards improvement in rTNSS in 100 micrograms, this did not reach statistical significance (LS mean difference =  $-0.452$ ,  $P=0.073$ , 95% CI  $-1.24$ ,  $-0.04$ ). Post-hoc analysis of efficacy data over 6 and 12 weeks from this study, and a 6 week HPA-axis safety study, each showed that the improvement in rTNSS for AVAMYS Nasal Spray 110 micrograms nasal spray over placebo was statistically significant.

A randomised, double-blind, parallel-group, multicenter, one-year placebo-controlled clinical growth study evaluated the effect of fluticasone furoate nasal spray 110 micrograms daily on growth velocity in 474 prepubescent children (5 to 7.5 years of age for girls and 5 to 8.5 years of age for boys) with stadiometry. Mean growth velocity over the 52-week treatment period was lower in the patients receiving fluticasone furoate ( $5.19\text{ cm/year}$ ) compared to placebo ( $5.46\text{ cm/year}$ ). The mean treatment difference was  $-0.27\text{ cm per year}$  [95% CI  $-0.48$  to  $-0.06$ ].

## **Pre-clinical Safety Data**

### **Carcinogenesis, mutagenesis**

There were no treatment-related increases in the incidence of tumours in two year inhalation studies in rats and mice.

AVAMYS Nasal Spray was not genotoxic *in vitro* or *in vivo*.

### **Reproductive toxicology**

The potential for reproductive toxicity was assessed in animals by inhalation administration to ensure high systemic exposure to fluticasone furoate. There were no effects on mating performance or fertility of male or female rats. In rats, developmental toxicity was confined to an increased incidence of incompletely ossified sternabrae in

association with lower foetal weight. High doses in rabbits induced abortion. These findings are typical following systemic exposure to potent corticosteroids. There were no major skeletal or visceral abnormalities in either rats or rabbits, and no effect on pre- or post-natal development in rats.

### **Animal toxicology and/or pharmacology**

Findings in general toxicology studies were similar to those observed with other glucocorticoids and are not considered to be clinically relevant to intranasal use of AVAMYS Nasal Spray.

## **PHARMACEUTICAL PARTICULARS**

### **List of Excipients**

Glucose Anhydrous (also known as Dextrose Anhydrous)

Microcrystalline Cellulose and Carboxymethylcellulose Sodium (also known as Dispersible Cellulose)

Polysorbate 80

Benzalkonium Chloride Solution

Disodium Edetate (also known as Edetate Disodium)

Purified Water

### **Incompatibilities**

None.

### **Shelf-Life**

The expiry date is indicated on the packaging.

### **Special Precautions for Storage**

Store below 30°C

Do not refrigerate or freeze.

### **Nature and Contents of Container**

AVAMYS Nasal Spray is a drug suspension contained within a glass bottle fitted with a metering spray pump, which is encased in an off-white plastic device with a blue side-actuated lever and lid.

The fill weight of the products are sufficient to deliver a minimum of 30 (sample pack), 60 or 120 sprays after priming.

Not all presentations are available in every country.

## Instructions for Use/Handling

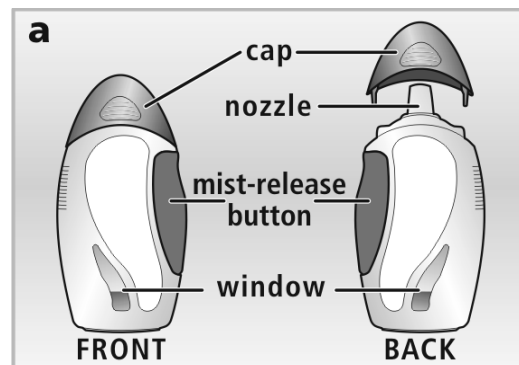
Patients should be instructed that the device must be primed before first use and re-primed if the cap is left off or the device does not seem to be working. In order to prime the device, the nasal spray needs to be shaken vigorously for about 10 seconds with the cap on. This is important as *AVAMYS* Nasal Spray is a thick suspension that becomes liquid when vigorously shaken. It will only spray when it becomes liquid. The patient must then press the button firmly all the way in, approximately 6 times until a fine mist is seen (to ensure a full dose is delivered). Once primed, the patient must shake the nasal spray vigorously each time before use. The cap must be replaced after use to keep the nozzle clean and to prevent the need for re-priming.

This section includes the following information:

- ❖ **The nasal spray**
- ❖ **6 important things you need to know about *AVAMYS* Nasal Spray**
- ❖ **Preparing the nasal spray**
- ❖ **Using the nasal spray**
- ❖ **Cleaning the nasal spray**

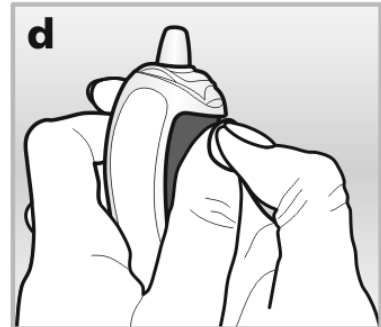
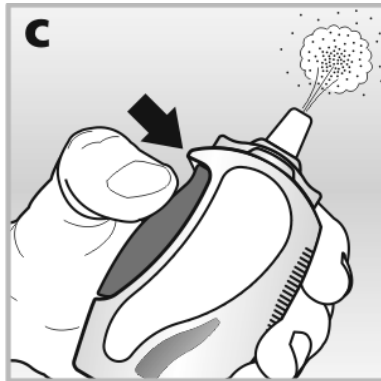
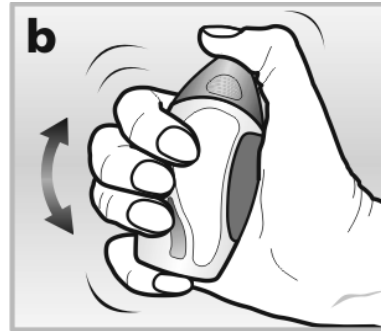
### The nasal spray

- Your medicine comes in a brown glass bottle inside a plastic casing. It will contain either 30, 60 or 120 sprays, depending on the pack size that has been prescribed for you (**picture a**).
- A window in the plastic casing allows you to see how much medicine is left. You will be able to see the liquid level for a new 30 or 60 spray bottle (**picture a**), but not for a new 120 spray bottle because the liquid level is above the window.
- The medicine sprays out of the nozzle when the button on the side is **pressed firmly all the way in**.
- A removable cap protects the nozzle from dust and prevents it from blocking up.



## Six important things you need to know about AVAMYS Nasal Spray

1. The nasal spray comes in a brown glass bottle. To check how much is left, **hold the nasal spray upright against a bright light**. You will then be able to see the level through the window.
2. When you **first use the nasal spray** you must **shake it vigorously** with the cap on for about 10 seconds. This is important as AVAMYS Nasal Spray is very thick and becomes more liquid when you shake it well (**picture b**). It will only spray when it becomes liquid.
3. The button on the side must be pressed firmly all the way in, to release a spray through the nozzle (**picture c**).
4. If you have difficulty pressing the button with your thumb, you can use two hands (**picture d**).
5. **Always keep the cap on the nasal spray** when you are not using it. The cap keeps the dust out, seals in the pressure and stops the nozzle from blocking up. When the cap is in place the button on the side can't be pressed accidentally.
6. **Never use a pin** or anything sharp to clear the nozzle. It will damage the nasal spray.



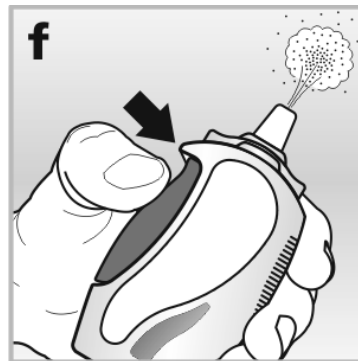
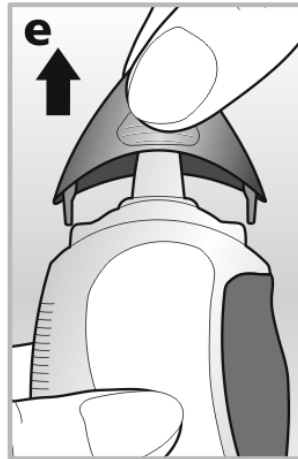
## Preparing the Nasal Spray

**You must prepare the nasal spray:**

- before you use it for the first time
- if you have left the cap off.

Preparing the nasal spray helps to make sure you always get the full dose of medicine. Follow these steps:

- With the cap on, **shake the nasal spray vigorously** for about 10 seconds.
- Remove the cap by gently squeezing the sides of the cap with your thumb and forefinger and pulling it straight off (**picture e**).
- Hold the nasal spray upright and point the nozzle away from you.
- **Press the button firmly all the way in. Do this at least 6 times** to release a fine spray into the air (**picture f**).
- The nasal spray is now ready for use.



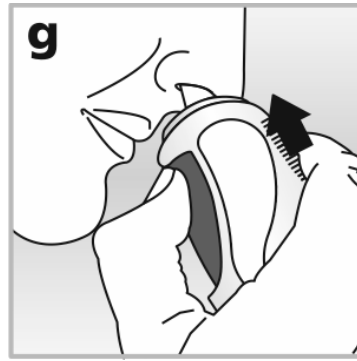
## Using the nasal spray

1. **Shake the nasal spray vigorously.**

2. Remove the cap.

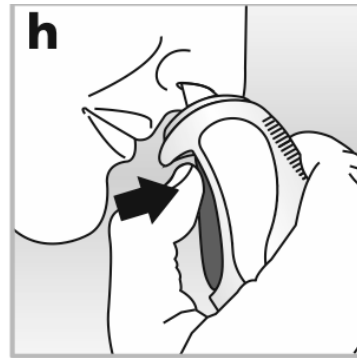
3. **Blow your nose** to clear your nostrils, and then tilt your head forward a little bit.

4. Hold the nasal spray upright and carefully place the nozzle in one of your nostrils (**picture g**).



5. Point the end of the nozzle toward the outside of your nose, away from the centre ridge of your nose. This helps direct the medicine to the right part of your nose.

6. As you breathe in through your nose, **press the button once firmly all the way in (picture h)**.



7. Be careful not to get any spray in your eyes. If you do, rinse your eyes with water.

8. Take the nozzle out and breathe out through your mouth.

9. If your doctor has told you to take 2 sprays per nostril, repeat steps 4 to 6.

10. Repeat steps 4 to 6 for your other nostril.

11. **Replace the cap** on the nasal spray.

### **Cleaning the nasal spray**

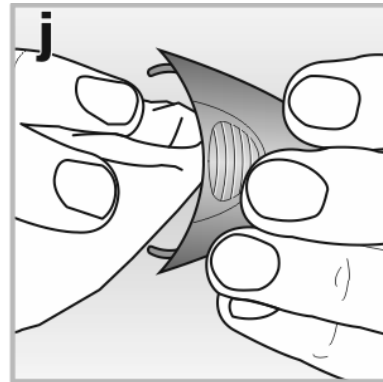
### After each use:

- Wipe the nozzle and the inside of the cap (**picture i and j**). Don't use water to do this. Wipe with a clean, dry tissue.
- **Never use a pin** or anything sharp on the nozzle.
- **Always replace the cap** once you have finished to keep out dust, seal in the pressure and stop the nozzle from blocking up.



If the nasal spray does not seem to be working:

- Check you still have medicine left. Look at the level through the window. If the level is very low there may not be enough left to work the nasal spray.
- Check the nasal spray for damage.
- If you think the nozzle may be blocked, **don't use a pin** or anything sharp to clear it.
- Try to reset it by following the instructions under 'Preparing the nasal spray for use'.
- If it is still not working, or if it produces anything other than a fine mist (such as a jet of liquid), or if you feel any discomfort using the spray, return it to your pharmacist.



### Manufactured by

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Barnard Castle  
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