AVAMYS ™ NASAL SPRAY
Fluticasone furoate

QUALITATIVE AND QUANTITATIVE COMPOSISTION

AVAMYS Nasal Spray is a white, uniform suspension contained in an amber glass bottle, fitted with a metering (50 µL) 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, Adolescents (12 years and over) and children (6-11 years)

Avamys is indicated for the treatment of:
the symptoms of 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, and the patient should be informed that their symptoms will improve with continuous regular use. The duration of treatment should be restricted to the period that corresponds to allergic exposure.

Populations

Adults/adolescents (12 years and older)

The recommended starting dosage is two 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 one spray in each nostril once daily (total daily dose, 55 micrograms) may be effective for maintenance. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Children (6 to 11 years)

The recommended starting dosage is one spray (27.5 micrograms per spray) in each nostril once daily (total daily dose, 55 micrograms). Patients not adequately responding to one spray in each nostril once daily (total daily dose, 55 micrograms) may use two sprays in each nostril once daily (total daily dose, 110 micrograms). Once adequate control of symptoms is achieved, dose reduction to one spray in each nostril once daily (total daily dose, 55 micrograms) is recommended.

Children (under 6 years of age)

The experience in children under the age of 6 years is limited. Safety and efficacy in this group has not been well established.

Elderly

No dosage adjustment required (see Pharmacokinetics)

Renal impairment

No dosage adjustment required (see Pharmacokinetics)

Hepatic impairment

No dosage adjustment required in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see Warnings and Precautions, and Pharmacokinetics)

The intranasal device should be shaken before use. The device is primed by pressing the mist release button for at least six spray actuations (until a fine mist is seen), whilst holding the device upright. Re-priming (approximately 6 sprays until a fine mist is seen) is only necessary if the cap is left off for 5 days or the intranasal device has not been used for 30 days or more. The device should be cleaned after each use and the cap replaced.

Contraindications
AVAMYS Nasal Spray is contraindicated in patients with hypersensitivity to any of the ingredients.

Warnings and Precautions
Fluticasone furoate undergoes extensive first-pass metabolism by the liver enzyme CYP3A4, therefore the pharmacokinetics of fluticasone furoate in patients with severe liver disease may be altered (see Interactions and Pharmacokinetics). 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 of nasal corticosteroid may occur, particularly at high doses prescribed for prolonged periods. These effects vary between patients and different corticosteroids. Treatment with higher that recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. Fluticasone furoate 110 micrograms once daily was not associated with hypothalamic-pituitary-adrenal (HPA) axis suppression in adult, adolescent or paediatric subjects. However the dose of intranasal fluticasone furoate should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.
Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained.

In addition, consideration should be given to referring the patient to a paediatric specialist. If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to fluticasone furoate.
Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.
Avamys Nasal Spray contains benzalkonium chloride. It may cause irritation of the nasal mucosa.

Interactions
Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the cytochrome P450 3A4. Based on data with another glucocorticoid (fluticasone propionate), that is metabolised by CYP3A4, coadministration with ritonavir is not recommended becuase of the risk of increased systemic exposure of fluticasone furoate. Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors as an increase in systemic exposure cannot be ruled out. In a drug interaction study of 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-h 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 outweight the potential risks to the foetus.

Fertility
There are no data in humans (see Nonclinical Information, Reproductive Toxicology)

Pregnancy
Following intranasal administration of fluticasone furoate at the maximum recommended human dose (110 mcg/day), plasma fluticasone furoate concentrations were typically non-quantifiable and therefore potential for reproductive

toxicity is expected to be very low (see Nonclinical Information, Reproductive Toxicology)

Lactation
The excretion of fluticasone furoate into human breast milk has not been investigated. Administration of fluticasone furoate to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

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 >1/10
Common >1/100 and <1/10
Uncommon >1/1000 and <1/100
Rare >1/10,000 and <1/1000
Very rare <1/10,000

Clinical Trial Data

Respiratory, thoracic and mediastinal disorders	
Very common :	Epistaxis
In adults and adolescents, the incidence of epitaxis 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 epitaxis was similar between *AVAMYS* Nasal Spray and placebo.	
Common:	Nasal ulceration

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

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 (<10 pg/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 the 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 17b-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 17b-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 (<10 pg/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were observed in <16% of paediatric patients following intranasal dosing of 110 micrograms once daily and only <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:-
A study of a single 400 microgram dose of oral inhaled fluticasone furoate in patients with moderate hepatic impairment resulted in increased Cmax (42%) and AUC(0-∞) (172%) and a modest (on overage 23%) decrease in cortisol levels in patients compared to healthy subjects. From this study the average predicted exposure for 110 micrograms of intranasal fluticasone furoate in patients moderate hepatic impairment would not be expected to result in suppression of cortisol. Therefore moderate hepatic impairment is not predicted to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment. The exposure of fluticasone furoate is likely to be further increased in such patients.

Other pharmacokinetic:-
Fluticasone furoate is typically not quantifiable (<10pg/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were only observed in <31% of patients aged 12 years and above and in < 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.

Seasonal Allergic Rhinitis : Primary and secondary key endpoints

Study	Primary Endpoint : Daily rTNSS		Secondary Endpoint: Daily rTOSS	
	LS Mean Difference	P-value (95% CI)	LS Mean Difference	P-value (95% CI)
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 = refelctive 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 8 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.

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 2 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 and nasal congestion. No significant differences were observed between 55 micrograms *AVAMYS* Nasal Spray and placebo 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 mcg 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, supported the efficacy of fluticasone furoate nasal spray 110 micrograms once daily. A 6-week study that assessed the effect of fluticasone furoate nasal spray 110 micrograms once daily on adrenal function in children aged 2 to 11 years showed that there was no significant effect on 24-hour serum cortisol profiles, compared with placebo. Results from a placebo controlled knemometry study of *AVAMYS* Nasal Spray 110 micrograms once daily observed no clinically relevant effects on short-term lower leg growth rate in children.

Pre-clinical Safety Data
Carcinogenesis, mutagenesis
There were no treatment-related increases in the incidence of tumours in 2 year inhalation studies in rats and mice. Fluticasone furoate 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 fluticasone furoate.

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 Precaution for storage
Store below 30°C
Do not refrigerate or freeze

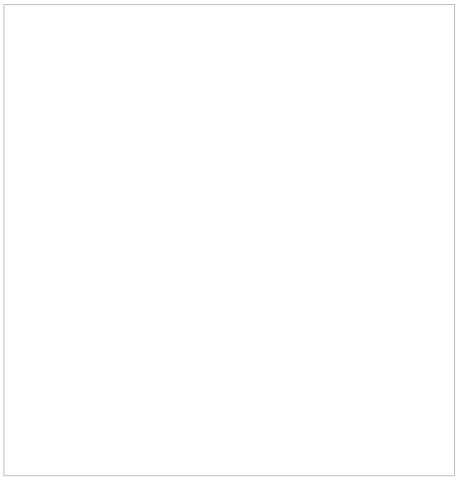
Nature and Contents of Container
AVAMYS Nasal Spray is a drug suspension contained within a glass bottle fitted with a metering spray pump, which is encased in an off-white plastic device with a blue side actuated lever and lid. The fill weight of the proposed commercial products are sufficient to deliver a minimum of 30 (sample pack), 60 or 120 sprays after priming.
Not all presentations are available in every country.

Instructions for Use/Handling
Once the device has been primed (approximately 6 sprays) each spray delivers 27.5 micrograms of active substance fluticasone furoate. Re-priming is only necessary if the cap is left off for 5 days or the nasal spray has not been used for 30 days or more.

1. The Nasal Spray
see figure a:

- Your medicine comes in a glass bottle inside a plastic casing
- A window on the side of the casing allows you to see how much medicine is left
- The medicine sprays out of the nozzle when the button on the side is firmly pressed
- The nozzle is protected by a removable cap

Figure a.



2. Testing the Nasal Spray

Figure b.

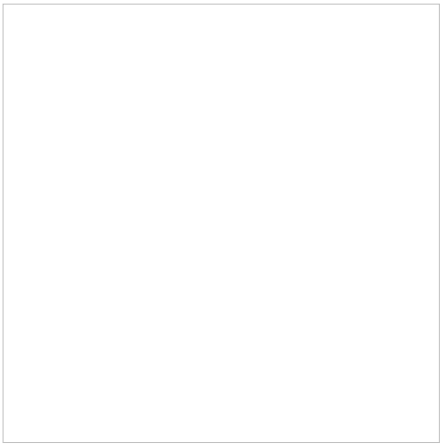
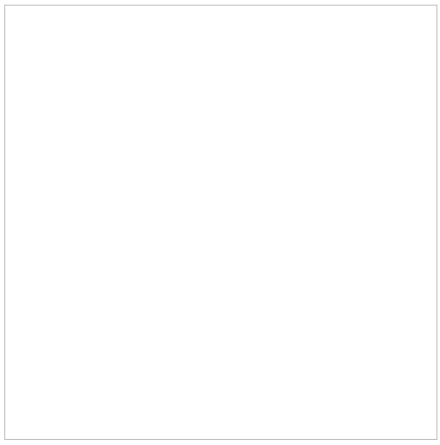


Figure c.



The first time you use the nasal spray, you must test that it is working properly. If you have left the cap off or have not used your spray for nearly a month, test it again.

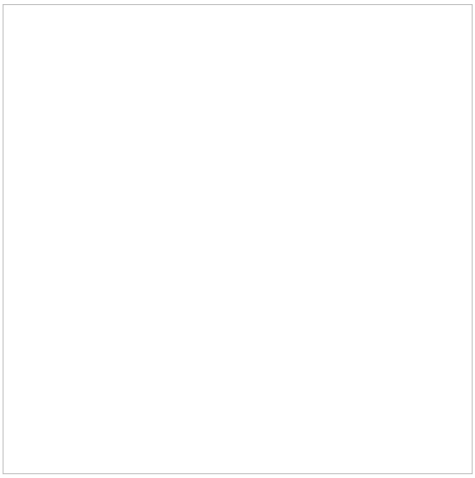
1. **With the cap on,** shake the nasal spray
2. **Remove the cap** by gently squeezing the sides of the cap with your thumb and forefinger and pulling it straight off - *see figure b.*
3. **Point the nozzle away** from you and firmly press the button on the side at least 6 times to release a fine spray into the air - *see figure c*
4. **The nasal spray is now ready for use**

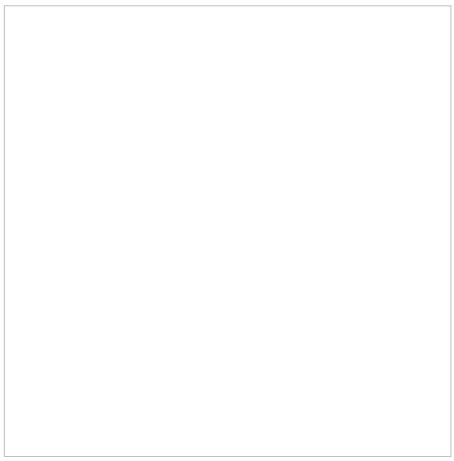
If you drop the spray, check for damage and test it again. If the spray is damaged, if it produces anything other than a fine mist (such as a jet of liquid), or if you feel any discomfort using the spray: **Return it to your pharmacist.**

3. How to use the Nasal Spray

Figure d.

Figure e.



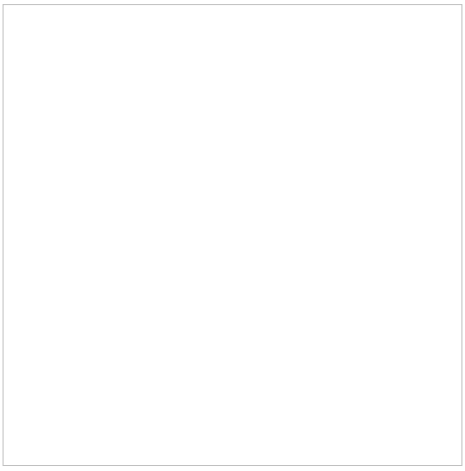


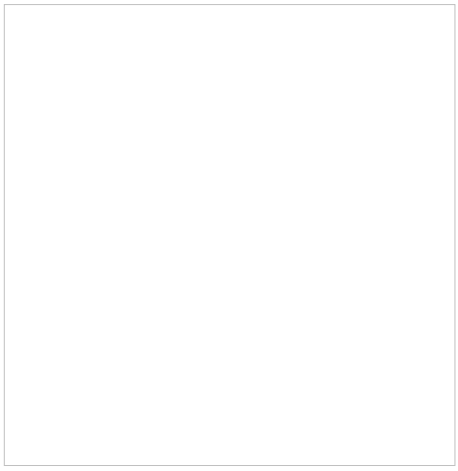
Blow your nose before you use the spray to clear your nostrils. Shake the spray gently before each use.

1. **Tilt your head forward** a little bit
2. **Hold the nasal spray upright** and carefully place the nozzle in one of your nostrils - *see figure d.*
3. P**oint the end of the nozzle toward the outside of your nose**, away from the centre ridge of your nose. This helps get the medicine to the right part of your nose.
4. **As you breathe in through your nose, firmly press the button once** to spray the medicine in your nose - *see figure e*
   Be careful not to get any spray in your eyes. If you do, rinse your eyes with water.
5. **Take the nozzle out and breathe out through you mouth**
6. **Repeat the previous 5 steps** for your other nostril
7. I**f your doctor has told you to take 2 sprays per nostril,** repeat all the 6 steps above.

4. Cleaning your Nasal Spray

Figure f. **Figure g.**





1. **After each use**, wipe the nozzle and the inside of the cap - *see figures f and g*
   Don't use water to do this, wipe with a clean, dry tissue
2. **Always replace the cap** once you have finished to keep out dust

5. If you use to much *AVAMYS* Nasal Spray

Talk to your doctor or pharmacist

6. **If you forget to use *AVAMYS* Nasal Spray**
- If you miss a dose, take it when you remember
- If it is nearly time for your next dose, wait until then. Do not take a double dose.

Avamys is a trademark of the GlaxoSmithKline group of companies

Box, Bottle contain 30 spray, Reg. No. xxxxxxxxxxxxxxxxxxxxxxx
Box, Bottle contain 60 spray, Reg. No. xxxxxxxxxxxxxxxxxxxxxxx
Box, Bottle contain 120 spray, Reg. No. xxxxxxxxxxxxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Reg. No. xxxxxxxxxxxxxxxxxxxxxxx

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