

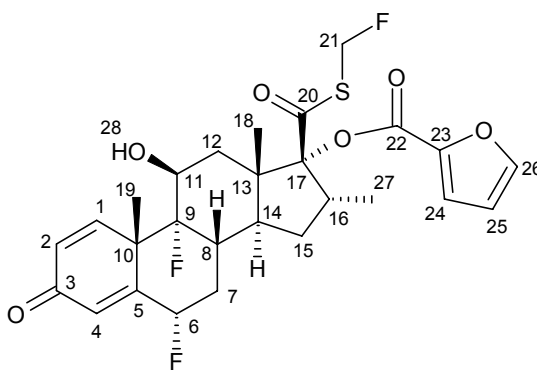
PRODUCT INFORMATION
(This PI contains all registered presentations of Avamys.)

AVAMYS[®] Nasal Spray

NAME OF THE MEDICINE:

Fluticasone furoate

Structure:



Chemical Name: Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6 α ,11 β ,16 α ,17 α)- (9Cl)

Molecular Formula: C₂₇H₂₉F₃O₆S

CAS Number: 397864-44-7

DESCRIPTION:

Fluticasone furoate is practically insoluble or insoluble in water, and slightly soluble in acetone, dimethylsulphoxide and ethanol.

Avamys Nasal Spray is a white suspension of micronised fluticasone furoate for topical administration to the nasal mucosa by means of a metering atomising spray pump. Each spray of the suspension delivers approximately 27.5 micrograms of micronised fluticasone furoate as an ex-device dose.

PHARMACOLOGY:

Pharmacodynamics:

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

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 (<10pg/mL). Fluticasone furoate has a low (0.50%) systemic bioavailability at intranasal doses of up to 2640 micrograms per day.

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 β -carboxylic metabolite, by the cytochrome P450 enzyme CYP3A4. The principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate function to form the 17 β -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 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 (<10pg/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 C_{max} (42%) and AUC_(0-∞) (172%) 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.

CLINICAL TRIALS:

Seasonal and Perennial Allergic Rhinitis in Adults and Adolescents (12 years and over):

Five randomised, double blind, parallel group, placebo-controlled trials have investigated the safety and efficacy of Avamys nasal spray 110 micrograms once daily in adults and adolescents 12 years of age and older with symptoms of seasonal or perennial allergic rhinitis. The five trials include one 2-week dose-ranging trial in patients with seasonal allergic rhinitis (FFR20001), three 2-week efficacy trials in patients with seasonal allergic

rhinitis (FFR30003, FFR103184, FFR104861), and one 4-week efficacy trial in patients with perennial allergic rhinitis (FFR30002).

The primary efficacy variable for all studies was based on the daily assessment of four nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) using a four-point (0 [none] to 3 [severe]) categorical scoring scale, with the maximum score being 12, called the total nasal symptom score (TNSS). The reflective TNSS (rTNSS) requires the patient to record symptom severity over the previous 12 hours; the instantaneous TNSS (iTNSS) requires the patient to record symptom severity at the time immediately prior to the next dose. Morning and evening rTNSS scores were averaged over the treatment period and the difference in placebo in the change from baseline rTNSS was the primary efficacy variable.

Additional key secondary efficacy variables were assessed, including mean change from baseline over the entire treatment period in AM pre-dose iTNSS, mean change from baseline over the entire treatment period in daily reflective total ocular symptom score (rTOSS) (applicable to the seasonal allergic rhinitis trials only, excluding FFR20001) and the patients' perception of overall response to therapy. The total ocular symptom score (TOSS) was calculated on the daily assessment of three ocular symptoms (itching/burning, tearing/watering, and redness) using a four-point (0 [none] to 3 [severe]) categorical scoring scale, with the maximum score being 9.

In the four seasonal allergic rhinitis trials, Avamys nasal spray 110 micrograms once daily significantly improved nasal symptoms (comprising rhinorrhea, nasal congestion, sneezing and nasal itching) and ocular symptoms (comprising itching/burning, tearing/watering and redness of the eyes) compared with placebo (see Table 1). The improvement was maintained over the full 24 hours after once daily administration as evaluated by AM pre-dose iTNSS (treatment effect ranged from, -0.902 to -1.898, $p < 0.001$ across the four studies). Similar improvement was observed for AM rTNSS and PM rTNSS and AM rTOSS and PM rTOSS suggesting consistent day time and night time relief of nasal and ocular symptoms.

Table 1: Seasonal Allergic Rhinitis - primary and secondary key endpoints

Study	Primary Endpoint: Daily rTNSS		Secondary Endpoint: Daily rTOSS	
	LS Mean Difference (95% CI)	p-value	LS Mean Difference (95% CI)	p-value
FFR20001	-2.012 (-2.58,-1.44)	<0.001	-	-
FFR30003	-0.777 (-1.28,-0.27)	0.003	-0.546 (-0.95,-0.14)	0.008
FFR103184	-1.757 (-2.28,-1.23)	<0.001	-0.741 (-1.14,-0.34)	<0.001
FFR104861	-1.473 (-2.01,-0.94)	<0.001	-0.600 (-1.01,-0.19)	0.004

rTNSS = reflective Total Nasal Symptom Scores (comprising rhinorrhea, nasal congestion, sneezing and nasal itching);

rTOSS = reflective Total Ocular Symptom Scores (comprising itching/burning, tearing/watering and redness of the eyes);

LS = Least square; LS mean difference = LS mean change from baseline in active – LS mean change from baseline in placebo;

CI = Confidence interval

Onset of action was experienced as early as 8 hours after initial administration. Significant improvement in symptoms was observed in the first 24 hours in all studies, and continued to improve over several days.

Avamys nasal spray significantly improved the patients' perception of overall response to therapy. Additionally, the patients' quality of life (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 ranged from -0.572 to -1.000, $p < 0.001$, [across the four studies).

In the perennial allergic rhinitis trial, Avamys nasal spray 110 micrograms once daily significantly improved nasal symptoms compared to placebo (mean change from baseline 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 patients' perception of overall response to therapy was significantly improved compared to placebo. Although numerical improvements in overall RQLQ scores with Avamys nasal spray 110 mcg were noted, these were not statistically significant when compared to placebo.

Data from the safety studies where efficacy was collected to measure compliance were supportive of the above results.

Seasonal and Perennial Allergic Rhinitis in Children (2 to 11 years of age):

The paediatric dose is based on assessment of the efficacy data across the allergic rhinitis population in children.

Two randomised, double blind, parallel group, placebo-controlled trials have investigated the safety and efficacy of Avamys nasal spray 55 micrograms and 110 micrograms once daily in the treatment of children 2 to <12 years of age with symptoms of seasonal or perennial allergic rhinitis.

In the seasonal allergic rhinitis trial (FFR100010) of 2 weeks duration, Avamys nasal spray 110 micrograms once daily 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 Avamys nasal spray 55 micrograms and placebo on any endpoint.

In the perennial allergic rhinitis trial (FFR30008) of 12 weeks duration, with the primary endpoint assessed over the first 4 weeks, Avamys nasal spray 55 micrograms once daily 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 with Avamys nasal spray 110 micrograms this did not reach statistical significance (LS mean difference = -0.452, $p = 0.073$, 95%CI -0.95, 0.04).

The above efficacy results are based on children 6 to <12 years of age. Efficacy in children 2 to <6 years of age was supported by a numerical decrease in the rTNSS.

INDICATIONS:

For the treatment of seasonal allergic rhinitis and perennial allergic rhinitis in adults and children of ages 2 years and older.

CONTRAINDICATIONS:

Avamys is contraindicated in patients with a history of hypersensitivity to any components of the preparations (see Presentation).

PRECAUTIONS:

Fluticasone furoate undergoes extensive first-pass metabolism by the liver enzyme CYP3A4, therefore the pharmacokinetics of intranasal fluticasone furoate in patients with severe liver disease may be altered. (see Interactions).

Local Infection: Infection of the nasal airways should be appropriately treated but does not constitute a contraindication to treatment with Avamys. After nasal surgery, healing must have occurred before use.

Rare instances of glaucoma and increased intra-ocular pressure have been reported following administration of intranasal corticosteroids, as a class effect.

Nasopharyngeal candidiasis can occur in patients treated with intranasal steroids, as a class effect. Special care should be taken when treating patients who may be susceptible to candida infections (eg diabetics).

Systemic effects/adrenocortical function

Intranasal steroid products are designed to deliver drug directly to the nasal mucosa in order to minimise overall systemic glucocorticoid exposure and side effects. Topical corticosteroids may be absorbed in amounts that can have systemic effects. Use of excessive doses may cause suppression of HPA function, reduction in bone density and retardation of growth rate in adolescents and children. Physicians should be alert for evidence of systemic effects, especially in chronically treated patients.

The lowest dose of Avamys that causes suppression of the HPA axis, effects on bone mineral density or growth retardation has not yet been established. However, the systemic bioavailability of fluticasone furoate is low (estimated at 0.50%) when given as Avamys and this limits the potential for systemic side effects. Measurement of serum cortisol concentrations in the clinical studies did not suggest any HPA axis suppression with recommended doses.

Use in Children:

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. Results from a placebo controlled knemometry study of fluticasone furoate 110 micrograms once daily observed no clinically relevant effects on short-term lower leg growth rate in children.

However, 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.

Effects on ability to drive and use machinery:

Fluticasone furoate is unlikely to produce an effect.

Effects on Fertility:

There were no effects on mating performance or fertility of male or female rats in which systemic exposure to fluticasone furoate was achieved by inhalational administration.

Carcinogenicity:

No evidence of a tumorigenic effect was observed in two year inhalational studies of fluticasone furoate in mice receiving doses of up to 18.8 µg/kg/day or in rats receiving up to 8.6 µg/kg/day. These doses were approximately 8.5- and 4-fold the human adult dose based on mg/kg, respectively.

Genotoxicity:

There was no evidence of a genotoxicity potential of fluticasone furoate in a standard battery of genotoxicity assays.

Use in Pregnancy: (Category B3)

There is insufficient evidence of safety of fluticasone furoate in human pregnancy. Systemically absorbed corticosteroids are known to induce fetotoxic and teratogenic effects in rodent studies. However, equivalent effects have not been reported when these compounds have been given to humans during pregnancy. Following intranasal administration of fluticasone furoate at the maximum recommended human dose (110 micrograms per day), plasma concentrations were typically non-quantifiable (see Pharmacokinetics). Fetal exposure and therefore potential for reproductive toxicity is expected to be very low. As with other compounds of this class, the use of Avamys during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Use in Lactation:

The excretion of fluticasone furoate into human breast milk has not been investigated. Related drugs are known to be excreted in the milk of lactating rats. However, plasma levels in patients following intranasal application of fluticasone furoate at recommended doses are low, and therefore the amount of fluticasone ingested by the newborn is likely to be very small.

Use in the Elderly:

No dosage adjustment required. (see Pharmacokinetics).

Interactions:**Interaction with other medicinal products and other forms of interaction**

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 concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 out of 20 subjects). This small increase in exposure did not result in 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 Precautions 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.

ADVERSE EFFECTS:

Fluticasone furoate nasal spray was well tolerated in adult, adolescent and paediatric subjects 2 years of age and older with seasonal allergic rhinitis and/or perennial allergic rhinitis over two- and six-week treatment periods. The compound was also well tolerated in longer term use over a period of 12 weeks in paediatric subjects and over a period of one year in adult and adolescent subjects.

Adverse Events

A summary of the adverse events occurring at an incidence of $\geq 3\%$ and more frequently in the fluticasone furoate than placebo group in the adult and adolescents perennial allergic rhinitis long-term safety study (FFR102123) is provided below:

Adverse Event	Number (%) of subjects	
	Placebo (N=201)	Fluticasone Furoate 110 μ g (N=605)
Nasopharyngitis	51 (25)	157 (26)
Epistaxis	17 (8)	123 (20)
Back pain	12 (6)	39 (6)
Cough	7 (3)	29 (5)
Toothache	5 (2)	29 (5)
Nausea	6 (3)	20 (3)
Pharyngitis	5 (2)	18 (3)
Diarrhoea	5 (2)	17 (3)
Bronchitis	4 (2)	17 (3)
Conjunctivitis	3 (1)	18 (3)
Nasal dryness	1 (<1)	17 (3)

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 $\geq 1/100$ and $<1/10$
- Uncommon $\geq 1/1000$ and $<1/100$
- Rare $\geq 1/10,000$ and $<1/1000$
- Very rare $<1/10,000$

Respiratory, thoracic and mediastinal disorders

Very Common: Epistaxis

Epistaxis was generally mild to moderate in intensity. In adults and adolescents, the incidence of epistaxis was higher in longer term use (more than six weeks) than in short term use (up to six weeks). In paediatric clinical studies of up to 12 weeks duration the incidence of epistaxis was similar between fluticasone furoate and placebo.

Common: Nasal ulceration

DOSAGE AND ADMINISTRATION:

Fluticasone furoate Nasal Spray is for administration by the intranasal route only.

For full therapeutic benefit regular usage is recommended. Onset of action has been observed as early as 8 hours after administration. It may take several days of treatment to achieve maximum benefit. An absence of an immediate effect should be explained to the patient.

Shake well before use. Remove cap. If using for the first time, prime the device with approximately 6 sprays (until a fine mist is seen). Each spray delivers 27.5 micrograms of the active substance fluticasone furoate. The cap must be replaced after use. 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.

For seasonal allergic rhinitis and perennial allergic rhinitis:

Adults/Adolescents (12 years and over)

The recommended starting dosage is two sprays (27.5 micrograms of fluticasone furoate 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.

Children (2 to 11 years of age)

The recommended starting dosage is one spray (27.5 micrograms of fluticasone furoate 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 2 years of age: There is no experience in children under the age of 2 years.

Special patient groups

Elderly Patients: No dosage adjustment required. (see Pharmacokinetics).

Renal Patients: No dosage adjustment required. (see Pharmacokinetics).

Hepatic Patients: No dosage adjustment is required at the indicated dosage in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment. (see Pharmacokinetics).

OVERDOSAGE:

In a bioavailability study, intranasal doses of up to 2640 micrograms per day were administered over three days with no adverse systemic effects observed. (see Precautions).

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

PRESENTATION:

Avamys Nasal Spray is a white suspension contained in an amber glass bottle fitted with a metering 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.

Avamys Nasal Spray also contains the following excipients: Glucose Anhydrous, Dispersible Cellulose, Polysorbate 80, Benzalkonium Chloride, Disodium Edetate, and Purified Water.

Avamys Nasal Spray: Available in 120, 60* and 30* spray packs.

* not currently sold

STORAGE CONDITIONS:

Store below 30°C. Do not refrigerate or freeze.

SPONSOR:

GlaxoSmithKline Australia Pty Ltd
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POISON SCHEDULE OF THE MEDICINE: Schedule 4 – Prescription Only Medicine

DATE OF TGA APPROVAL: 31 January 2008

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