SCHEDULING STATUS:
S4

PROPRIETARY NAME AND DOSAGE FORM:
AVAMYS Nasal Spray (Suspension)

COMPOSITION:
Each 50 µl spray contains 27.5 µg of fluticasone furoate.

Preservative: Benzalkonium chloride 0.015% m/m.

PHARMACOLOGICAL CLASSIFICATION:
A 21.5.1 Corticosteroids and analogues.

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
Fluticasone furoate is a synthetic trifluorinated corticosteroid that possesses a high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action.

Pharmacokinetic properties
Absorption: Fluticasone furoate undergoes incomplete absorption and extensive first-pass metabolism in the liver and gut resulting in negligible systemic exposure. The intranasal dosing of 110 µg once daily does not typically result in measurable plasma concentrations (<10 pg/ml). The absolute bioavailability for intranasal fluticasone furoate administered as 880 µg three times per day (2 640 µg 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 58.7 L/h) from systemic circulation principally by hepatic metabolism to an inactive 17β-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 17β-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.

Children:
Fluticasone furoate is typically not quantifiable (<10 pg/ml) following intranasal dosing of 110 µg once daily. Quantifiable levels were observed in <16% of paediatric patients following intranasal dosing of 110 µg once daily and only <7% of paediatric patients following 55 µg 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).
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 with the younger subjects.

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 µg dose of oral inhaled fluticasone furoate in patients with moderate hepatic impairment resulted in increased Cmax (42%) and AUC(0-∞) (172%) compared to healthy subjects. From this study the average predicted exposure for 110 µg 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.

INDICATIONS:
Adults/Adolescents (12 years and over)
Treatment of the symptoms of seasonal allergic rhinitis:
In patients with seasonal allergic rhinitis, AVAMYS nasal spray is indicated in the treatment of nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) and ocular symptoms (itching/burning, tearing/watering, and redness of the eye).

Treatment of the symptoms of perennial allergic rhinitis:
In patients with perennial allergic rhinitis, AVAMYS nasal spray is indicated in the treatment of nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing).

Children (2 to 11 years)
Treatment of the symptoms of seasonal allergic rhinitis:
In patients with seasonal allergic rhinitis, AVAMYS nasal spray is indicated in the treatment of nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing).

Treatment of the symptoms of perennial allergic rhinitis:
In patients with perennial allergic rhinitis, AVAMYS nasal spray is indicated in the treatment of nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing).

CONTRA-INDICATIONS:
Hypersensitivity to the active substance or to any of the excipients of AVAMYS nasal spray.

WARNINGS:
If there is any reason to suppose that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to fluticasone furoate.

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 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 hour serum cortisol levels between the two groups.
Based on data with another glucocorticoid metabolised by CYP3A4 co-administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate.

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.

PREGNANCY AND LACTATION:
Safety and efficacy of AVAMYS in pregnancy and lactation has not been established.

DOSEAGE AND DIRECTIONS FOR USE:
AVAMYS nasal spray is for administration by the intranasal route only.

Shake the nasal spray before use.

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.

Once the device has been primed (approximately 6 sprays until a fine mist is seen) each spray delivers 27.5 µg 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.

Seasonal allergic rhinitis and perennial allergic rhinitis:

Adults/Adolescents (12 years and over)
The recommended starting dosage is two sprays (27.5 µg of fluticasone furoate per spray) in each nostril once daily (total daily dose: 110 µg).

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

Children (2 to 11 years of age)
The recommended starting dosage is one spray (27.5 µg of fluticasone furoate per spray) in each nostril once daily (total daily dose: 55 µg).

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

Children under 2 years of age: There is no experience in children under the age of 2 years.

Elderly Patients: The normal adult dosage is applicable.

Renal Patients: The normal adult dosage is applicable.

Hepatic Patients: The normal adult dosage is applicable in mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Side effects:
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 $\geq$ 1/1 000 and <1/100
- Rare $\geq$ 1/10 000 and <1/1 000
- Very rare <1/10 000.

### Clinical Trial Data

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Common</td>
<td>Nasal ulceration</td>
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</tbody>
</table>

Epistaxis was generally mild to moderate in intensity. 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 patients receiving fluticasone furoate and patients receiving placebo.

### Special 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.

Fluticasone furoate has a negligible (0.50%) systemic bioavailability at intranasal doses of up to 24 times the recommended adult daily dose (2 640 µg per day). 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 than 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 µg once daily was not associated with 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 are maintained.

Results from a placebo controlled knemometry study of fluticasone furoate 110 µg once daily observed no clinically relevant effects on short-term lower leg growth rate in children.

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.

### 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 fluticasone furoate.

### KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In a bioavailability study, intranasal doses of up to 2 640 µg per day were administered over three days with no adverse systemic effects observed. Acute overdose is unlikely to require any therapy other than observation.
IDENTIFICATION:
A predominantly off white, side-actuated plastic device with a light blue lever and lid containing a stopper. The device contains an amber glass bottle fitted with a metering atomising spray pump, filled with a white uniform suspension.

PRESENTATION:
The nasal spray container consists of an inner container within an outer device. The inner container consists of a Type I amber glass bottle, closed with a metering spray pump. The outer device is a predominantly off white side-actuated plastic delivery system with a light blue lever and lid containing a stopper. The product is available in three pack sizes:

- 30 sprays with a target net content of 4.5 g
- 60 sprays with a target net content of 6.5 g
- 120 sprays with a target net content of 10 g.

STORAGE INSTRUCTIONS:
Store below 30 ºC. Do not refrigerate or freeze.

Keep out of reach of children.

REGISTRATION NUMBER:
41/21.5.1/0968

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
GlaxoSmithKline South Africa (Pty) Ltd
57 Sloane Street
Bryanston
2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
4 December 2008
PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SCHEDULING STATUS:
S4

PROPRIETARY NAME AND DOSAGE FORM:
AVAMYS Nasal Spray (Suspension)

COMPOSITION OF THE MEDICINE, THAT IS, WHAT THIS MEDICINE CONTAINS:
- The active substance is fluticasone furoate. Each 50 µl of nasal spray contains 27.5 µg of fluticasone furoate.
- The other ingredients are glucose anhydrous, dispersible cellulose, polysorbate 80, benzalkonium chloride (preservative), disodium edetate, purified water.

APPROVED INDICATION AND USE, THAT IS, WHAT THIS MEDICINE IS USED FOR:
- AVAMYS contains the medicine fluticasone furoate. It is a ‘glucocorticoid’ which helps decrease inflammation in the nose and irritation of the eyes caused by allergies (rhinitis). The effects are usually felt within the first day, although some people will not feel the full effects until several days after first taking it.
- The doctor has prescribed it to help treat symptoms caused by allergies, including watery and itchy eyes, and stuffy or runny nose, and sneezing. Symptoms can occur at specific times of the year and be caused by allergies to pollen from grass or trees (hayfever) or they can occur all year around and be caused by allergies to animals, house-dust mites or moulds. Taking AVAMYS once daily will help prevent both daytime and night time symptoms.
- AVAMYS is delivered into the nose as a fine mist spray. AVAMYS is not for use in the eyes. There is a window on the side of the outer plastic cover of AVAMYS so that you can see how much medicine is left in the nasal spray bottle. Ask your doctor for more medicine when the amount of medicine left is getting low.

INSTRUCTION BEFORE TAKING THE MEDICINE:
Do not use AVAMYS if:
You are allergic (hypersensitive) to fluticasone furoate or any of the other ingredients of AVAMYS.

Take special care with AVAMYS:
Taking other medicines
- Please tell your doctor if you are taking or have recently taken any other medicines. This includes medicines for asthma, injected or oral steroids, or any medicines obtained without a prescription.
- Tell your doctor if you are taking an antiviral medicine called a protease inhibitor (e.g. ritonavir) or a type of medicine used to treat fungal infections (e.g. ketoconazole). Your doctor will assess whether you should take AVAMYS with these medicines.
**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, talk with your doctor before taking AVAMYS. Your doctor will assess whether you can take AVAMYS during this time.

**Driving and using machines**
AVAMYS is unlikely to affect your ability to drive and use machines.

**INSTRUCTIONS ON HOW TO TAKE THE MEDICINE:**
Take your AVAMYS once every day as close to the same time of day as possible to treat your symptoms throughout the day and night.

**Adults and adolescents 12 years and older**
- The usual starting dose is 2 sprays in each nostril once every day.
- Once symptoms are controlled you may be able to decrease your dose to 1 spray in each nostril once every day.

**Children**
- In children aged 2 to 11 the usual starting dose is 1 spray in each nostril once every day.
- If symptoms are very bad the doctor may increase the dose to 2 sprays in each nostril once every day until symptoms are under control. It may then be possible for the dose to be reduced to 1 spray in each nostril once every day.
- AVAMYS is not recommended for use in children below 2 years of age.

**Instructions for use**
Once the device has been primed (approximately 6 sprays) each spray delivers 27.5 µg 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.
2. Testing the nasal spray

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

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. Point 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. If your doctor has told you to take 2 sprays per nostril, repeat all the 6 steps above.

4. Cleaning your nasal spray

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.

If you take more AVAMYS than you should

It is important to take AVAMYS as you have been instructed. If you accidently take more than the recommended number of sprays, talk to your doctor or pharmacist.

If you forget to take AVAMYS

If you forget to take your AVAMYS, take a dose when you remember or, if it is near the time for your next dose, wait until then. Do not take a double dose to replace the one you forgot.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

SIDE EFFECTS:

Possible side effects are listed below:

**Very common** (affects more than 1 person in 10)
You may have minor nosebleeds whilst using AVAMYS, particularly if you are using it for more than 6 weeks continuously.

**Common** (affects less than 1 person in 10)
The inside of your nose may feel irritated or uncomfortable and may get streaks of blood when you blow your nose. This may be due to nasal ulceration.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

STORAGE AND DISPOSAL INFORMATION:

- **Keep out of reach of children.**
- Store below 30 °C.
- Do not keep AVAMYS in the fridge or freezer.
Once opened, you can use AVAMYS up until the last day of the month of the expiry date. Do not use AVAMYS after the expiry date which is stated on the label or carton.

Medicines should not be disposed of via wastewater or household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

PRESENTATION:
The nasal spray container consists of an inner container within an outer device. The inner container consists of a Type I amber glass bottle, closed with a metering spray pump. The outer device is a predominantly off white side-actuated plastic delivery system with a light blue lever and lid containing a stopper. The product is available in three pack sizes:

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