GENEMIST

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GENEMIST 27,5 µg/spray, nasal spray suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 µl spray contains 27,5 µg of fluticasone furoate.

Preservatives: benzalkonium chloride 0,015 % *m/m* and disodium edetate 0,015 % *m/m.*

Excipient with known effect:

Benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension.

A white uniform suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents (12 years and over):

Treatment of the symptoms of seasonal allergic rhinitis:

In patients with seasonal allergic rhinitis, GENEMIST nasal spray is indicated in the treatment of nasal symptoms (rhinorrhoea, 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, GENEMIST nasal spray is indicated in the treatment of nasal symptoms (rhinorrhoea, 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, GENEMIST nasal spray is indicated in the treatment of nasal symptoms (rhinorrhoea, nasal congestion, nasal itching and sneezing).

Treatment of the symptoms of perennial allergic rhinitis:

In patients with perennial allergic rhinitis, GENEMIST nasal spray is indicated in the treatment of nasal symptoms (rhinorrhoea, nasal congestion, nasal itching and sneezing).

4.2 Posology and method of administration

Posology

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.

Seasonal allergic rhinitis and perennial allergic rhinitis:

Adults and 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: No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Method of administration:

GENEMIST nasal spray is for administration by the intranasal route only.

Shake the nasal spray before use.

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 fluticasone furoate 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.

4.3 Contraindications

Hypersensitivity to fluticasone furoate or to any of the excipients of GENEMIST nasal spray listed in section 6.1.

4.4 Special warnings and precautions for use

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.
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 are less likely to occur than with oral corticosteroids and may 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 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.

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 µg daily for one year (see section 4.8). Therefore, children should be maintained on the lowest dose which delivers adequate symptom control (see section 4.2).

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.

Medical practioners should be alert to the risk that potential systemic steroid effects including ocular changes, such as central serous chorioretinopathy may occur.

GENEMIST contains benzalkonium chloride (see section 6.1). Long-term use may cause oedema of the nasal mucosa.

4.5 Interaction with other medicines and other forms of interaction

Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the cytochrome P450 3A4. In an 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 medicines.

4.6 Fertility, pregnancy and lactation

Safety and efficacy of GENEMIST in pregnancy and lactation has not been established.

There are no fertility data in humans.

4.7 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 GENEMIST.

4.8 Undesirable 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 ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1 000 and <1/100, rare ≥1/10 000 and <1/1 000, very rare <1/10 000, not known (cannot be estimated from the available data).

Clinical trial data:

Respiratory, thoracic and mediastinal disorders	
Very common	Epistaxis
Common	Nasal ulceration
Musculoskeletal and connective tissue disorders	
Not known	Growth retardation in children
Eye disorders	
Not known	Vision blurred (see section 4.4)

Description of selected adverse reactions:

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 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.

Growth retardation:

In a one-year clinical study assessing growth in pre-pubescent children receiving 110 µg of GENEMIST once daily, an average treatment difference of -0,27 cm per year in growth velocity was observed compared to placebo.

Post-marketing data:

Immune system disorders:

Rare: hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria

Nervous system disorders:

Common: headache

Respiratory, thoracic and mediastinal disorders:

Uncommon: rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness

Very rare: nasal septum perforation.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of GENEMIST is important. It allows continued monitoring of the benefit/risk balance of GENEMIST. Health care providers are asked to report any suspected adverse reactions to: SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.5.1 Corticosteroids and analogues.

Pharmacotherapeutic group: Nasal preparations, corticosteroids.

ATC code: R01AD12.

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

5.2 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 µg/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 µg /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:

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 µg dose of oral 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 µg) 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 µg). Based on these findings the average predicted exposure for 110 µg of intranasal fluticasone furoate in this patient population would not be expected to result in suppression of cortisol.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose anhydrous

Dispersible cellulose

Polysorbate 80

Purified water

Benzalkonium chloride

Disodium edetate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 ºC in the container specified.

Do not refrigerate or freeze.

6.5 Nature and contents of container

The nasal spray container consists of an inner container within an outer device. The inner container consists of a Type I or Type III 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 outer plastic cover has a window for viewing the bottle contents.

GENEMIST 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER

41/21.5.1/0967

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 June 2009

10. DATE OF REVISION OF THE TEXT

18 March 2021

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