

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Azelastine /Fluticasone Substipharm 125 micrograms+50 micrograms per actuation nasal spray, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of suspension contains 1000 micrograms azelastine hydrochloride and 365 micrograms fluticasone propionate

One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride equivalent to 125 micrograms azelastine and 50 micrograms fluticasone propionate.

Excipient with known effect:

One actuation (0.14 g) delivers 0.014 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension.

White, to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.

4.2 Posology and method of administration

Posology

For full therapeutic benefit regular usage is essential.

Contact with the eyes should be avoided.

Adults and adolescents (12 years and older)

One actuation in each nostril twice daily (morning and evening).

Children below 12 years

[Product name] is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Elderly

No dose adjustment is required in this population.

Renal and hepatic impairment

There are no data in patients with renal and hepatic impairment.

Duration of treatment

[Product name] is suitable for long-term use.

The duration of treatment should correspond to the period of allergenic exposure.

Method of administration

[Product name] is for nasal use only.

Instruction for use

Preparing the spray:

The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards. Prior to first use [Product name] must be primed by pressing down and releasing the pump 6 times. If [Product name] has not been used for more than 7 days it must be reprimed once by pressing down and releasing the pump.

Using the spray:

The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards.

After blowing the nose the suspension is to be sprayed once into each nostril keeping the head tilted downward (see figure). After use the spray tip is to be wiped and the protective cap to be replaced.



4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see section 4.5).

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses 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. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

[Product name] undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events. Caution is advised when treating these patients.

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.

In general, the dose of intranasal fluticasone formulations should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. Higher doses than the recommended one (see section 4.2) have not been tested for [Product name]. 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 nasal corticosteroids at recommended doses. Regular monitoring of height growth in children, and also adolescents, who are on long-term treatment with nasal corticosteroids are recommended. If growth is slowed, treatment should be reconsidered aiming at reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Careful monitoring is required in patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts.

If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to [Product name].

In patients who have tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth, the possible benefits of the treatment with [Product name] should be weighed against possible risk.

Infections of the nasal airways should be treated with antibacterial or antimycotical therapy, but do not constitute a specific contraindication to treatment with [Product name].

Excipient(s) with known effect:

[Product name] contains benzalkonium chloride. It may cause oedema of the nasal mucosa.

4.5 Interaction with other medicinal products and other forms of interaction

Fluticasone propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products is also expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable

reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate.

Azelastine hydrochloride

No specific interaction studies with azelastine hydrochloride nasal spray have been performed. Interaction studies at high oral doses have been performed. However, they bear no relevance to azelastine nasal spray as given recommended nasal doses result in much lower systemic exposure. Nevertheless, care should be taken when administering azelastine hydrochloride in patients taking concurrent sedative or central nervous medications because sedative effect may be enhanced. Alcohol may also enhance this effect (see section 4.7).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women. Therefore, [Product name] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3)

Breastfeeding

It is unknown whether nasally administered azelastine hydrochloride metabolites or fluticasone propionate metabolites are excreted in human breast milk. [Product name] should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant (see section 5.3).

Fertility

There are only limited data with regard to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[Product name] has minor influence on the ability to drive and use machines.

In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, can occur when using [Product name]. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

4.8 Undesirable effects

Commonly, dysgeusia, a substance-specific unpleasant taste, may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration).

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

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 ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Frequency	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very rare</i>	<i>Not known</i>
System Organ Class						

<i>Immune system disorders</i>					Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm	
<i>Nervous system disorder</i>		Headache, Dysgeusia (unpleasant taste), unpleasant smell			Dizziness, somnolence (drowsiness, sleepiness)	
<i>Eye disorders*</i>					Glaucoma, increased intraocular pressure, cataract	Vision, blurred (see also section 4.4)
<i>Respiratory, thoracic and mediastinal disorders</i>	Epistaxis		Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation**, mucosal erosion	Nasal ulcers
<i>Gastrointestinal disorders</i>				Dry mouth	Nausea	
<i>Skin and subcutaneous tissue disorders</i>					Rash, pruritus, urticaria	
<i>General disorders and administration site conditions</i>					Fatigue (weariness, exhaustion), weakness (see section 4.7)	

* A very small number of spontaneous reports have been identified following prolonged treatment with intranasal fluticasone propionate.

** Nasal septal perforation has been reported following the use of intranasal corticosteroids.

Systemic effects of some nasal corticosteroids may occur, particularly when administered at high doses for prolonged periods (see section 4.4).

In rare cases osteoporosis was observed if nasal glucocorticoids were administered long-term.

Paediatric population

Growth retardation has been reported in children receiving nasal corticosteroids. Growth retardation may be possible in adolescents, too (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

No overdose reactions are expected with nasal administration.

No patient data are available regarding the effects of acute or chronic intranasal overdose fluticasone propionate.

Intranasal administration of 2 milligrams fluticasone propionate (10 times the recommended daily dose) twice daily for seven days to healthy human volunteers has shown no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

Administration of higher doses than those recommended over a long period of time may lead to temporary suppression of adrenal function.

In these patients, treatment with [Product name] should be continued at a dose sufficient to control symptoms; the adrenal function recovers after a few days and can be verified by measuring plasma cortisol.

In case of overdose after incidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) caused by azelastine hydrochloride are to be expected based on the results of animal experiments.

Treatment of these disorders must be symptomatic. Depending on the amount swallowed, gastric lavage is recommended. There is no known antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, corticosteroids/ fluticasone, combinations, ATC code: R01AD58.

Mechanism of action

[Product name] contains azelastine hydrochloride and fluticasone propionate, which have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhinoconjunctivitis symptoms.

Fluticasone propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid that has a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action, e.g. 3-5 fold more potent than dexamethasone in cloned human glucocorticoid receptor binding and gene expression assays.

Azelastine hydrochloride

Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H₁-antagonist, mast cell stabilizing and anti-inflammatory properties. Data from *in vivo* (preclinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late-stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin.

Relief of nasal allergic symptoms is observed within 15 minutes after administration.

Clinical efficacy and safety

In 4 clinical studies in adults and adolescents with allergic rhinitis azelastine hydrochloride/fluticasone propionate one spray in each nostril twice daily significantly improved nasal symptoms (comprising rhinorrhoea, nasal congestion, sneezing and nasal itching) compared with placebo, azelastine hydrochloride alone and fluticasone propionate alone. Azelastine hydrochloride/fluticasone propionate significantly improved ocular symptoms (comprising itching, tearing/watering and redness of the eyes) and the patients' disease-related quality of life (Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ) in all 4 studies.

In comparison to a marketed fluticasone propionate nasal spray, substantial symptom improvement (50% reduction in nasal symptoms severity) was achieved significantly earlier (3 days and more) with azelastine hydrochloride/fluticasone propionate. The superior effect of azelastine hydrochloride/fluticasone propionate to fluticasone propionate nasal spray was maintained throughout one-year study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

An exposure study of allergens with ambrosia pollen showed the first statistically significant relief of nasal symptoms 5 minutes after administration of azelastine hydrochloride/fluticasone propionate (compared to placebo). At 15 minutes after administration of azelastine hydrochloride/fluticasone propionate, 60% of patients reported a clinically relevant reduction in symptom scores of at least 30%.

5.2 Pharmacokinetic properties

Absorption

After intranasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) of azelastine hydrochloride/fluticasone propionate, the mean ($\pm$ standard deviation) peak plasma exposure (C_{max}) was 194.5 ± 74.4 pg/mL for azelastine and 10.3 ± 3.9 pg/mL for fluticasone propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97.7 ± 43.1 pg/mL*hr for fluticasone propionate. The median time to peak exposure (t_{max}) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone propionate.

Fluticasone systemic exposure was ~50% increased comparing azelastine hydrochloride/fluticasone propionate with a marketed fluticasone propionate nasal spray. Azelastine hydrochloride/fluticasone propionate was equivalent to a marketed azelastine nasal spray with respect to azelastine systemic exposure. There was no evidence of pharmacokinetic interactions between azelastine hydrochloride and fluticasone propionate.

Distribution

Fluticasone propionate has a large volume of distribution at steady-state (approximately 318 liters). Plasma protein binding is 91%.

The volume of distribution of azelastine is high indicating distribution predominantly into the peripheral tissue. The level of protein binding is 80-90%. Additionally, both drugs have broad therapeutic windows. Therefore, drug displacement reactions are unlikely.

Biotransformation

Fluticasone propionate is rapidly cleared from systemic circulation, mainly by hepatic metabolism into an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Azelastine is metabolized into *N*-desmethylazelastine via various CYP isoenzymes, mainly CYP3A4, CYP2D6 and CYP2C19.

Elimination

The elimination rate of intravenous administered fluticasone propionate is linear over the 250-1000 microgram dose range and are characterized by a high plasma clearance ($CL=1.1$ l/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8 h terminal half-life. The renal clearance of fluticasone

propionate is negligible (<0.2%) and less than 5% is cleared as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile. Plasma elimination half-lives after a single dose of azelastine are approximately 20-25 hours for azelastine and about 45 hours for the therapeutically active metabolite *N*-desmethy laz elastine. Excretion occurs mainly via the faeces. The sustained excretion of small amounts of the dose in the faeces suggests that some enterohepatic circulation may occur.

5.3 Preclinical safety data

Fluticasone propionate

Findings in general toxicology studies were similar to those observed with other glucocorticoids and are associated with exaggerated pharmacological activity. These results are not likely to be relevant for humans given that recommended nasal doses result in minimal systemic exposure. No genotoxic effects of fluticasone propionate have been observed in conventional genotoxicity tests. In addition, there were no treatment-related increases on incidence of tumours in two-year inhalation studies in rats and mice.

In animal studies glucocorticoids have been shown to induce malformations including cleft palate and intra-uterine growth retardation. Again, this is not likely to be relevant for humans given that recommended nasal doses result in minimal systemic exposure (see section 5.2).

Azelastine hydrochloride

Azelastine hydrochloride displayed no sensitizing potential in the guinea pig. Azelastine demonstrated no genotoxic potential in a battery of in vitro and in vivo tests, nor any carcinogenic potential in rats or mice. In male and female rats, azelastine at oral doses greater than 3 mg/kg/day caused a dose-related decrease in the fertility index.

No substance-related alterations were found in the reproductive organs of males or females during chronic toxicity studies, however, embryotoxic and teratogenic effects in rats, mice and rabbits occurred only at maternal toxic doses (for example, skeletal malformations were observed in rats and mice at doses of 68.6 mg/kg/day).

Azelastine hydrochloride/fluticasone propionate

Repeated-dose intranasal toxicity studies in rats for a period up to 90 days and in dogs for 14 days with azelastine hydrochloride/fluticasone propionate revealed no new adverse effects in comparison to the individual components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Glycerol
Microcrystalline cellulose
Carmellose sodium
Polysorbate 80
Benzalkonium chloride
Phenylethyl alcohol
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

In-use shelf-life (after use): 6 months

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Type I amber glass bottle fitted with a spray pump, a nasal polypropylene applicator (actuator) and a dust cap, containing 23 g (at least 120 actuations) suspension.

Pack sizes:

1 bottle with 23 g suspension in 25 mL bottles (at least 120 actuations)

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-04-24