SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nasofan Aqueous 50 microgram Nasal Spray.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 microlitre metered spray contains 50 micrograms of fluticasone propionate.

Excipient(s) with known effect:

Each metered spray contains 40 micrograms of benzalkonium chloride solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, Suspension.

The medicinal product consists of a white, opaque aqueous suspension contained within an amber glass multidose bottle fitted with a metering pump.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nasofan Aqueous 50 microgram Nasal Spray is indicated in adults and children aged 4 years and older for the prophylaxis and treatment of seasonal allergic rhinitis (including hay fever) and perennial rhinitis.

4.2 Posology and method of administration

Posology

Paediatric population

The safety and efficacy of Nasofan Aqueous 50 micrograms Nasal Spray in children aged less than 4 years has not been established.

Adults and children of 12 years of age and over:

Two sprays into each nostril once a day (200 mcg), preferably in the morning is recommended. In some cases two sprays into each nostril twice a day (400 mcg) may be required. Once symptoms are under control a maintenance dose of one spray per nostril once a day (100 mcg) may be used. If symptoms recur the dosage may be increased accordingly. The maximum daily dose should not exceed four sprays into each nostril (400 mcg). The minimum dose at which the effective control of symptoms is maintained should be used.

Elderly patients:

The normal adult dosage is applicable.

Children between ages of 4 and 11:

One spray into each nostril once a day (100 mcg), preferably in the morning, is recommended. In some cases one spray into each nostril twice a day (200 mcg) may be required. The maximum daily dose should not exceed two sprays into each nostril (200 mcg). The minimum dose at which the effective control of symptoms is maintained should be used.

For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient since maximum relief may not be obtained for 3 to 4 days after commencement of treatment.

Method of administration

Nasofan Aqueous 50 microgram Nasal Spray is for administration by the intranasal route only.

Precautions to be taken before handling or administering the medicinal product

Prior to first use Nasofan Aqueous 50 microgram Nasal Spray must be primed by pressing down and releasing the pump six times. If Nasofan Aqueous 50 microgram Nasal Spray has not been used for 7 days it must be reprimed by pressing down and releasing the pump a sufficient number of times until a fine mist is produced.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Administration of treatment may be necessary for several days for the full benefit of Nasofan Aqueous 50 microgram Nasal Spray to be achieved.

Upon transferring patients from systemic steroid treatment to Nasofan Aqueous 50 microgram Nasal Spray care must be taken if there is any reason to suppose that their adrenal function is impaired.

Systemic Effects of Corticosteroids
Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed 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). Please refer to section 5.1 and 5.2.

Adrenal suppression may occur to clinically significant levels as a result of treatment with higher than recommended doses of nasal corticosteroids. 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 (see section 5.1 for data on intranasal fluticasone propionate).

Incidences of significant interactions between fluticasone propionate and potent inhibitors of the cytochrome P450 3A4 system (e.g. ketoconazole and protease inhibitors such as ritonavir) may occur. Increased systemic exposure to fluticasone propionate may result (e.g. Cushing's syndrome and adrenal suppression have been observed). Therefore concomitant use of fluticasone propionate and ritonavir should be avoided unless the expected benefit exceeds the possible risk of systemic adverse reaction of corticosteroids (see section 4.5).

Visual disturbance
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.

In most cases Nasofan Aqueous 50 microgram Nasal Spray will control seasonal allergic rhinitis, however in the event of an abnormally heavy challenge of summer allergens appropriate additional therapy may be necessitated in certain instances. Such an instance may particularly be to control eye symptoms.

Infections

In patients who have tuberculosis, any type of untreated infection, ocular herpes or have had a recent surgical operation or injury to the nose or mouth, the possible benefits of the treatment should be weighed against possible hazards.

Local infections: infections of the nasal airways should be appropriately treated but do not constitute a specific contraindication to treatment with Nasofan Aqueous 50 microgram Nasal Spray.

Paediatric population

Some nasal corticosteroids have been reported to produce growth retardation in children when prescribed at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If slowed growth is observed, a review of the therapy should be performed with a resultant reduction of the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. Furthermore a referral of the patient to a paediatric specialist should be considered.

Excipient(s):

Benzalkonium chloride

Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are obtained by intranasal use due to a significant first pass metabolism and high systemic clearance remedied by cytochrome P450 3A4 in the gut and liver. Thus, clinically significant interactions associated with fluticasone propionate are not commonly found.

Effects of fluticasone propionate on other drugs

No significant effect of fluticasone propionate on the pharmacokinetics of terfenadine and erythromycin has been shown during drug interaction studies.

Effects of other drugs on fluticasone propionate

No significant effect of terfenadine and erythromycin on the pharmacokinetics of fluticasone propionate has been shown during drug interaction studies.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is 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.

An interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can increase plasma concentration of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. After marketing, cases of clinically significant drug interactions have been reported in patients receiving fluticasone propionate intranasal or by inhalation, leading to systemic side effects, including Cushing syndrome and adrenal suppression. The simultaneous use of fluticasone propionate and ritonavir should therefore be avoided unless the benefits to the patient outweigh the risk of systemic side effects caused by corticosteroids.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of safety in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high systemic exposure; direct intranasal application ensures minimal systemic exposure.

As with other drugs the use of Nasofan Aqueous 50 microgram Nasal Spray during human pregnancy requires that the possible benefits of the drug be weighed against the possible hazards.

Breast-feeding

The secretion of fluticasone propionate in human breast milk has not been investigated. Subcutaneous administration of fluticasone propionate to lactating laboratory rats produced measurable plasma levels and evidence of fluticasone propionate in the milk. However, following intranasal administration to primates, no drug was detected in the plasma, and it is therefore unlikely that the drug would be detectable in milk. When Nasofan Aqueous 50 microgram Nasal Spray is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

4.7 Effects on ability to drive and use machines

Nasofan Aqueous 50 microgram Nasal Spray has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported side effects were epistaxis (≥ 1/10) followed by headache, unpleasant taste and smell, dryness and irritation of the nose, dryness and irritation of the pharynx (≥ 1/100 to < 1/10).

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Event	Frequency
Immune system disorders	Hypersensitivity reactions with the following manifestations:	
	Bronchospasm	Rare
	Anaphylactic reactions	Rare
	Anaphylactoid reactions	Rare
	Cutaneous hypersensitivity reaction	Very rare
	Angioedema (mainly facial and oropharyngeal oedema)	Very rare
Nervous system disorders	Headache, unpleasant taste, unpleasant smell.	Common
Eye disorders	Glaucoma, raised intraocular pressure, cataract These events have been identified from spontaneous reports following prolonged treatment.	Very rare
	Vision, blurred (see also section 4.4)	Not known
Respiratory, Thoracic & Mediastinal disorders	Epistaxis	Very common
	Nasal dryness, nasal irritation, throat dryness, throat irritation.	Common
	Nasal septal perforation*, mucocutaneous ulceration Usually in patients who have had previous nasal surgery.	Very rare
	Nasal ulcers	Not known

*Cases of perforation of the nasal septal wall have been reported as a result of the use of corticosteroids.

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

Paediatric population
Some nasal corticosteroids have been reported to produce growth retardation in children when prescribed at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored (please refer to section 4.4).

Reporting of suspected adverse reactions
Reporting of 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are no data available on the effects of acute or chronic overdose with Nasofan Aqueous 50 microgram Nasal Spray. Intranasal administration of 2 milligrams fluticasone propionate twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

Inhalation or oral administration of high doses of corticosteroids over a long period may lead to suppression of HPA axis function.

In these patients, the dose should be gradually reduced and treatment with Nasofan Aqueous 50 microgram Nasal Spray continued at a dosage sufficient to control the symptoms. The adrenal cortex function is restored within a few days, which can be verified by measuring plasma cortisol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, Corticosteroids.
ATC code: R01A D08

Clinical efficacy and safety
Fluticasone propionate administered nasally has a potent anti-inflammatory effect. Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio1.01, 90%CI 0.9-1.14).

Paediatric population
In a 1-year randomised, double-blind, placebo-controlled, parallel group growth study in pre-pubescent children aged 3 to 9 years (56 patients receiving intranasal fluticasone propionate and 52 receiving placebo) no statistically significant difference in growth velocity was observed in patients receiving intranasal fluticasone propionate (200 micrograms per day nasal spray) compared to placebo. The estimated growth velocity over one year of treatment was 6.20 cm/year (SE=0.23) in the placebo group and 5.99 cm/year (SE=0.23) in the fluticasone propionate group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% CI= -0.35, 0.76). No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

5.2 Pharmacokinetic properties

Absorption
Following intranasal dosing of fluticasone propionate, (200mcg/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest Cmax observed was 0.017ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

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

Biotransformation
Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate.

Elimination
The elimination rate of intravenous administered fluticasone propionate is linear over the 250 -1000mcg dose range and are characterised by a high plasma clearance (CL=1.1L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid

metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

5.3 Preclinical safety data

Toxicology and reproduction studies, as well as teratogenic studies, have shown only class effects typical of potent corticosteroids in higher doses than recommended. Fluticasone propionate is without mutagenic activity *in vitro* as well as *in vivo* and exhibits no carcinogenic potential in rodents. It does not irritate or sensitise animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose
Dispersible Cellulose
Phenylethyl Alcohol
Benzalkonium Chloride solution (40 micrograms per delivered dose)
Polysorbate 80
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After the first use: 3 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

12ml or 15ml amber glass bottle [Type III] fitted with an atomising metering pump.

Pack sizes: 60, 120, 150, 240 (2 bottles each containing 120 sprays) and 360 (3 bottles each containing 120 sprays) metered sprays.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 00530/0745

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Date of first authorisation: 12/05/2005
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07/09/2022