For the use only of registered medical practitioners or a hospital or a laboratory

Mometasone Aqueous Nasal Spray IP

NASONEX®

1. NAME OF THE MEDICINAL PRODUCT

NASONEX® Nasal Spray Suspension
Brand of Mometasone Furoate I.P. monohydrate

For INTRANASAL ADMINISTRATION

2. COMPOSITION

NASONEX® Nasal Spray Suspension is a metered-dose, manual pump spray unit containing a suspension of Mometasone Furoate I.P. Each metered dose pump actuation of NASONEX® Nasal Spray Suspension delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate as monohydrate equivalent to 50 micrograms mometasone furoate.

Inactive ingredients:
Microcrystalline Cellulose & Carboxymethylcellulose Sodium, Glycerin, Citric Acid, Sodium Citrate, Polysorbate 80, Benzalkonium Chloride and Water Purified.

Action: Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active.

3. DOSAGE FORMS

NASONEX® Nasal Spray Suspension is a non-pressurized metered dose nasal sprays designed for local nasal administration.

4. INDICATIONS

NASONEX® Nasal Spray Suspension is indicated for use in adults and children 12 years of age and older to treat the symptoms of seasonal allergic or perennial rhinitis.

NASONEX® Nasal Spray Suspension is also indicated for use in children 2 to 11 years of age to treat the symptoms of seasonal allergic or perennial allergic rhinitis.

In adults and children 12 years of age and older who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with

NASONEX® Nasal Spray Suspension may be initiated up to four weeks prior to the anticipated start of the pollen season.

NASONEX® Nasal Spray Suspension is indicated for the treatment of nasal polyps in adults 18 years of age and older.

5. DOSE, METHOD OF ADMINISTRATION AND USAGE

After initial priming of the NASONEX® Nasal pump (10 actuations, until a uniform spray is observed), each actuation delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent to 50 micrograms mometasone furoate. If the spray pump has not been used for 14 days or longer, it should be reprimed with 2 actuations, until a uniform spray is observed, before next use.

Shake container well before each use.

Seasonal allergic or perennial rhinitis: Adults (including geriatric patients) and adolescents: The usual recommended dose for prophylaxis and treatment is two sprays (50 micrograms/spray) in each nostril once daily (total dose 200 micrograms). Once symptoms are controlled, dose reduction to one spray in each nostril (total dose 100 micrograms) may be effective for maintenance. If symptoms are inadequately controlled, the dose may be increased to a maximum daily dose of four sprays in each nostril (total dose 400 micrograms). Dose reduction is recommended following control of symptoms.

Clinically significant onset of action occurs as early as within 12 hours after the first dose.

Children between the ages of 2 and 11 years: The usual recommended dose is one spray (50 micrograms/spray) in each nostril once daily (total dose 100 micrograms).

Administration to young children should be aided by an adult

Nasal Polyposis: Adults (including geriatric patients) and adolescents 18 years of age and older:
The usual recommended dose for polyposis is two sprays (50 micrograms/spray) in each nostril twice daily (total daily dose of 400 mcg). Once symptoms are adequately controlled, dose reduction to two sprays in each nostril once daily (total daily dose 200 mcg) is recommended.

6. USE IN SPECIAL POPULATIONS

There are no adequate or well-controlled studies in pregnant women. As with other nasal corticosteroid preparations NASONEX® should not be used in pregnant women or nursing mothers unless the potential benefit justifies the potential risk to the mother, fetus or infant. Infants born of mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

7. CONTRA-INDICATIONS

Hypersensitivity to any ingredients of NASONEX® Nasal Spray Suspension.

8. WARNINGS AND PRECAUTIONS

NASONEX® Nasal Spray Suspension should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex.

Following 12 months of treatment with NASONEX® Nasal Spray Suspension, there was no evidence of atrophy of the nasal mucosa; also, mometasone furoate tended to reverse the nasal mucosa closer to a normal histologic phenotype. As with any long-term treatment, patients using NASONEX® Nasal Spray Suspension over several months or longer should be examined periodically for possible changes in the nasal mucosa, including the development of nasal ulcerations. If localized fungal infection of the nose or pharynx develops, discontinuation of NASONEX® Nasal Spray Suspension therapy or appropriate treatment may be required.

There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX® Nasal Spray Suspension. However, as with other corticosteroids, patients who are transferred from long-term administration of systemically active corticosteroids to NASONEX® Nasal Spray Suspension require careful attention. Systemic corticosteroid withdrawal in such patients may result in adrenal insufficiency. If these patients exhibit signs and symptoms of adrenal insufficiency or symptoms of withdrawal (e.g., joint and/or muscular pain, lassitude, and depression initially), appropriate measures should be instituted.

Patients receiving corticosteroids who are potentially immunosuppressed should be warned of the risk of exposure to certain infections (e.g., chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs.

Following the use of intranasal corticosteroids, instances of nasal septum perforation or increased intraocular pressure have been reported very rarely.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) 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 of visual disturbances 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.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Rarely, immediate hypersensitivity reactions may occur after intranasal administration of mometasone furoate monohydrate. Very rarely, anaphylaxis and angioedema have been reported for NASONEX® Nasal Spray Suspension. Disturbances of taste and smell have been reported very rarely.

Acute Rhinosinusitis
If signs or symptoms of severe bacterial infection are observed (such as fever, persistent severe unilateral facial/tooth pain, orbital or peri-orbital facial swelling, or worsening of symptoms after an initial improvement), the patient should be advised to consult their physician immediately.

Safety and efficacy of NASONEX® Nasal Spray Suspension for the treatment of symptoms of rhinosinusitis in children under 12 years of age have not been studied.

Safety and efficacy of NASONEX® Nasal Spray Suspension for the treatment of nasal polyposis in children and adolescents less than 18 years of age have not been studied.

9. DRUG INTERACTIONS

Mometasone furoate via NASONEX® Nasal Spray Suspension has been administered concomitantly with loratadine with no effect on plasma concentrations of loratadine or its major metabolite. In these studies, mometasone furoate plasma concentrations were not detectable using an assay with a LLOQ of 50 pg/ml. The combination therapy was well tolerated

Mometasone furoate is metabolized by CYP3A4.

Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased plasma concentrations of corticosteroids and potentially increase the risk for systemic corticosteroid side-effects. Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side-effects.

10. UNDESIRABLE EFFECTS

Clinical Trials Experience
Note: Adverse events included are based on age and indication in local approvals. Those cited below are for the adult rhinitis studies. Similar findings were observed for the pediatric and adjunctive treatment for sinusitis studies. Treatment-related local adverse events reported in clinical studies with MFNS include headache (8%), epistaxis (*i.e.*, frank bleeding, blood-tinged mucus, and blood flecks) (8%), pharyngitis (4%), nasal burning (2%), and nasal irritation (2%), and nasal ulceration (1%), which are typically observed with use of a corticosteroid nasal spray. Epistaxis was generally self-limiting and mild in severity, and occurred at a higher incidence compared to placebo (5%), but at a comparable or lower incidence compared to the active control nasal corticosteroids studied (up to 15%).

In patients treated for acute rhinosinusitis, the overall incidence of adverse events was comparable to placebo and similar to that observed for patients with allergic rhinitis.

Nasal Polyposis: In patients treated for nasal polyposis, the overall incidence of adverse events was comparable to placebo and similar to that observed for patients with allergic rhinitis.

Post-Market Experience
The following additional adverse reactions have been reported in post-marketing use with NASONEX: vision blurred.

11. OVERDOSE

Because the systemic bioavailability is <1% (using a sensitive assay with a lower quantitation limit of 0.25 pg/ml) after administration of mometasone furoate via NASONEX® Nasal Spray, overdose is unlikely to require any therapy other than observation

12. PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active.

The precise mechanism of action is unknown, but it is likely that much of the mechanism for the anti-allergic and anti-inflammatory effects of mometasone furoate lies in its ability to inhibit the release of mediators of allergic reactions. Mometasone furoate significantly inhibits the release of leukotrienes from leucocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6, and TNFα; it is also a potent inhibitor of the production of the TH_2 cytokines, IL-4 and IL-5, from human CD4+ T-cells. In mixed leukocytes from atopic patients, mometasone furoate was a more potent inhibitor of leukotriene production than BDP.
In a preclinical model, mometasone furoate has been shown to reduce the accumulation of eosinophils markedly at the site of an allergic reaction. Additionally, mometasone furoate reduced the number of lymphocytes and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

Preclinical pharmacokinetics and metabolism

Several studies were conducted to investigate for mometasone furoate the absorption, distribution, metabolism and excretion following various routes of administration and in different species. Mometasone furoate and/or its metabolites are rapidly and extensively distributed in the rat. Mometasone furoate undergoes extensive first-pass metabolism and is excreted as metabolites mostly via the bile, and to a limited extent into the urine.

Preclinical safety data

No toxicologic effects unique to mometasone furoate exposure were demonstrated during the course of preclinical testing. All observed effects are typical of this class of compounds and are related to exaggerated pharmacologic effects of glucocorticoids.

Preclinical studies demonstrate that mometasone furoate is devoid of androgenic, anti-androgenic, estrogenic or anti-estrogenic activity but, like other glucocorticoids, it exhibits some anti-uterotrophic activity and delays vaginal opening in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day.

Mometasone furoate was non-mutagenic in the mouse-lymphoma assay and the Salmonella/E. coli/mammalian microsome mutagenicity bioassay. At cytotoxic doses only, mometasone furoate produced an increase in chromosome aberrations in vitro in Chinese hamster ovary cell (CHO) cultures in the non-activation phase, but not in the presence of rat liver S9 fraction. However, mometasone furoate did not induce chromosomal aberrations in vitro in a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, or in vivo in the mouse bone-marrow erythrocyte-micronucleus assay, in the rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes. The finding of simple chromosomal aberrations in the non-activation phase of the CHO assay is considered to be related to cytotoxicity and is not considered to be of significance in the risk assessment of mometasone furoate because of the negative results in the S9 phase of this assay, the negative results in a second in vitro chromal aberrations assay (CHL assay), and the negative results in three *in vivo* chromosomal aberrations assays.

In studies of reproductive function, subcutaneous mometasone furoate was well tolerated at doses up to 7.5 µg/kg. At 15 µg/kg, mometasone furoate caused prolonged gestation and prolonged and difficult labor occurred with a reduction in offspring survival and body weight or body weight gain. There was no effect on fertility.

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical and/or subcutaneous routes. Effects noted were umbilical hernia in rats, cleft palate in mice, and gall bladder agenesis, umbilical hernia, and flexed front paws in rabbits. There were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice.

In an oral teratology study in rabbits, at 700 µg/kg, increased incidences of resorption and malformations, including cleft palate and/or head malformations (hydrocephaly or domed head) were observed. Pregnancy failure was observed in most rabbits at 2800 µg/kg.

The carcinogenicity and toxicological potential of inhaled mometasone furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25 to 2.0 µg/l was investigated in studies in mice and rats of up to 24 months. Typical glucocorticoid-related effects, including several non-neoplastic lesions, were observed. No statistically significant dose-response relationship was detected for any of the tumor types.

While mometasone furoate has been shown to be a potent topical glucocorticoid, there is little systemic activity following intranasal administration. This is because of the low systemic bioavailability of the intranasal suspension, especially in man where systemic exposure is < 1% at the clinical dose (200 µg/day).

Clinical Pharmacology

Pharmacokinetic properties

Mometasone furoate monohydrate, administered as an aqueous nasal spray, has a systemic bioavailability of <1% in plasma, using a sensitive assay with a lower quantitation limit (LLOQ) of 0.25 pg/ml. Mometasone furoate suspension is very poorly absorbed from the gastrointestinal tract, and the small amount that may be swallowed and absorbed undergoes extensive first-pass hepatic metabolism prior to excretion in urine and bile.

Pharmacodynamic properties

In studies utilizing nasal antigen challenge, mometasone furoate in NASONEX® Nasal Spray Suspension has shown anti-inflammatory activity in both the early- and late- phase allergic responses. This has been demonstrated by decreases (vs. placebo) in histamine and eosinophil activity and reductions (vs. baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins. Because of the low systemic availability of mometasone furoate after intranasal administration, any pharmacodynamic correlations have to be based upon sensitive indices of possible systemic exposure rather than measured MF levels. Systemic activity of exogenous corticosteroids is commonly expressed by evaluating the hypothalamic-pituitary-adrenal (HPA) axis activity.

In two trials with 1954 patients 12 years of age and older, NASONEX® Nasal Spray Suspension 200 mcg twice daily was effective in significantly improving symptoms of rhinosinusitis compared to placebo as evaluated by the Major Symptom Score (MSS) composite of symptoms (facial pain/pressure/tenderness, sinus headache, rhinorrhea, post nasal drip, and nasal congestion/stuffiness) during the 15 day treatment period (P02683 $p < 0.001$; P02692 $p = 0.038$). A 500 mg three times a day amoxicillin arm was not significantly different from placebo in reducing the symptoms of rhinosinusitis as evaluated by the MSS. Fewer subjects treated with NASONEX® Nasal Spray Suspension 200 mcg twice daily were considered by the treating physician to be treatment failures than those with placebo ($p=0.0074$). In addition, during the post-treatment follow-up period, the number of recurrences seen with NASONEX® Nasal Spray Suspension was low and comparable to the amoxicillin and placebo treatment groups. Treatment duration beyond 15 days was not evaluated in acute rhinosinusitis.

In clinical trials with nasal polyposis NASONEX® Nasal Spray Suspension showed significant improvement when compared to placebo in the clinically relevant endpoints of congestion, nasal polyp size and loss of smell.

13. SHELF LIFE

Shelf life of mometasone furoate 50 mcg nasal suspension is 36 months

14. STORAGE:

Store below 30°C. Do not freeze.

15. PACKAGING INFORMATION

Available as pack of 140 metered actuations.

Patient's Instructions for Use:

SHAKE WELL BEFORE EACH USE

NASONEX®
(Mometasone furoate monohydrate)
Nasal Spray Suspension, 50 mcg*

*calculated on the anhydrous basis

This package insert is updated based on worldwide product circular no. S-CCDS-MK0887-NS-082017

Shake the bottle well before each use. Read complete instructions carefully and use only as directed.

1. Remove the plastic cap (Figure 1).

Figure 1

2. The very first time the spray is used, prime the pump by pressing downward on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb (Figure 2). **The actuator does not need to be pierced in order for the unit to function.** Press down and release the pump ten times or until a fine spray appears. DO NOT spray into eyes. The pump is now ready to use. The pump may be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by spraying two times or until a fine spray appears.

Figure 2

3. Gently blow your nose to clear the nostrils. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril (Figure 3). DO NOT spray directly onto nasal septum, the wall between the two nostrils.

Figure 3

4. For each spray, press firmly downward once on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril (Figure 4).

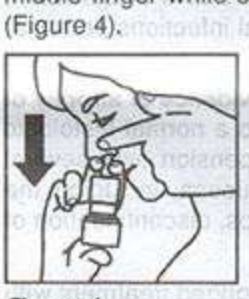

Figure 4

5. Then breathe out through the mouth.
6. Repeat in the other nostril.
7. Wipe the nasal applicator with a clean tissue and replace the plastic cap.

Pediatric Use: Administration to young children should be aided by an adult. The **Patient's Instructions for Use**, Steps 1 to 7 should be followed. The correct amount of medication in each spray can only be assured up to 120 sprays from the bottle even though the bottle is not completely empty. You should keep track of the number of sprays used from each bottle of NASONEX® Nasal Spray Suspension, 50 mcg and discard the bottle after using 120 sprays.

Cleaning: Please see **Applicator Cleaning Instructions**.

NASONEX® Nasal Spray Suspension, 50 mcg should not be sprayed into the eyes. Spraying NASONEX® Nasal Spray Suspension, 50 mcg directly onto the nasal septum should be avoided.

Store below 30°C. Do not freeze. **Protect from light. When NASONEX® Nasal Spray Suspension, 50 mcg is removed from its cardboard container, prolonged exposure of the product to direct light should be avoided. Brief exposure to light, as with normal use, is acceptable.**

SHAKE WELL BEFORE EACH USE.

APPLICATOR CLEANING INSTRUCTIONS:

NASONEX®
(Mometasone furoate monohydrate)
Nasal Spray Suspension, 50 mcg*

*calculated on the anhydrous basis

1. To clean the nasal applicator, remove the plastic cap (Figure 1).

Figure 1

2. Pull gently upward on the white nasal applicator so that it comes free (Figure 2).

Figure 2

3. Soak the nasal applicator in cold tap water and/or rinse both ends of the nasal applicator under cold tap water and dry (Figure 3). **Do not try to unblock the nasal applicator by inserting a pin or other sharp object.**

Figure 3

4. Rinse the plastic cap under cold water and dry (Figure 4).

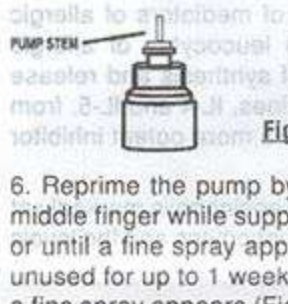

Figure 4

5. Reassemble the nasal applicator being certain the pump stem is reinserted into the applicator's center hole (Figure 5).

Figure 5

6. Reprime the pump by pressing downward on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb. Press down and release the pump two times or until a fine spray appears. DO NOT spray into eyes. The pump is now ready to use. The pump may be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by spraying two times or until a fine spray appears (Figure 6).

Figure 6

7. Replace the plastic cap (Figure 7).

Figure 7

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