NASONEX® Aqueous Nasal Spray

Brand of mometasone furoate monohydrate

FOR INTRANASAL ADMINISTRATION

DESCRIPTION: NASONEX Aqueous Nasal Spray is metered-dose, manual pump spray unit containing a suspension of mometasone furoate. Each metered-dose pump actuation of NASONEX Aqueous Nasal Spray delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent to 50 micrograms mometasone furoate.

Inactive ingredients: Cellulose, glycerol, citric acid monohydrate, sodium citrate dihydrate, polysorbate 80, benzalkonium chloride and purified water. Preservatives: benzalkonium chloride 0.2 mg/g.

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

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY: Preclinical studies demonstrate that mometasone furoate is devoid of androgenic, antiandrogenic, estrogenic or antiestrogenic activity but, like other glucocorticoids, it possesses some antiuterotrophic activity and delays vaginal opening in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day.

In cell culture, mometasone furoate was shown to be at least ten times more potent than other steroids, including beclomethasone dipropionate (BDP), betamethasone, hydrocortisone and dexamethasone, at inhibiting the synthesis/release of IL-1, IL-6 and TNFα . Mometasone furoate (IC_{50} = 0.12 Nm) was also at least six times more potent than BDP and betamethasone at inhibiting IL-5 production. Also, in mixed leukocytes from atopic patients, mometasone was a more potent leukotriene production inhibitor than BDP.

In a preclinical model, the compound has been shown to reduce the accumulation of eosinophils markedly at the site of an allergic reaction. For example, in allergic mice with IgE-mediated allergy, inhaled mometasone furoate at doses as low as 10 micrograms/kg inhibited eosinophil infiltration into bronchoalveolar lavage fluid and the lung bronchi and bronchioles. Additionally, mometasone furoate reduced the number of lymphocytes, and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

It is likely that much of the mechanism for the antiallergic 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 leukocytes of allergic patients. In addition, it is an extremely potent inhibitor of the production of the Th_2 cytokines, IL-4 and IL-5 from human CD4+ T-cells.

Mometasone furoate was nonmutagenic in the mouse-lymphoma assay and the salmonella/mammalian-microsome bioassay. Mometasone furoate was negative in the mouse bone-marrow erythrocyte-micronucleus assay, the rat bone-marrow clastogenicity assay, the mouse mitotic male germ-cell clastogenicity assay, and the Chinese hamster lung-cell chromosomal-aberrations assay. At cytotoxic doses in Chinese hamster ovary cell cultures, mometasone furoate induced a dose-related increase in simple chromosome aberrations when continuously exposed (7.5 hours) in the nonactivation phase, but not in the presence of rat liver S9 fraction. This finding is not considered to be of significance in the risk assessment of mometasone furoate, since the S9 phase of the chromosomal-aberration assay and all *in vivo* assays were negative. Clastogenic responses without human health risk implications have been observed at cytotoxic doses with other corticosteroids, such as dexamethasone.

In subcutaneous Segment I and III studies, mometasone furoate was well tolerated at doses up to 7.5 micrograms/kg (2.6 times the human dose by inhalation). At 15 micrograms/kg 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 topical (dermal) and/or subcutaneous routes. Umbilical hernia occurred in rats administered ≥ 600 micrograms/kg dermally, cleft palate in mice administered 180 micrograms/kg subcutaneously, and gall-bladder agenesis, umbilical hernia, and flexed front paws in rabbits administered ≥ 150 micrograms/kg dermally. In these teratogenicity studies, 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.

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

CLINICAL PHARMACOLOGY: Mometasone furoate, administered as a 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 metabolism prior to excretion in urine and bile.

In studies utilizing nasal antigen challenge, NASONEX Aqueous Nasal Spray 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 eosinophils, neutrophils, and epithelial cell adhesion proteins.

Three studies were conducted to assess the safety and efficacy of NASONEX Aqueous Nasal Spray in the treatment of nasal polyps for four months. These included two pivotal trials evaluating doses of 200 mcg once or twice daily and a supportive trial evaluating a dose of 200 mcg once daily. A total of 594 adult patients (ages 18 to 86 years) received NASONEX Aqueous Nasal Spray. The co-primary efficacy endpoints in the pivotal trials were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by nasal endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day. Improvement in other symptoms of nasal polyps (loss of smell, rhinorrhea and postnasal drip) was also observed after a 1-month treatment with 200 mcg, twice daily dose compared to placebo in both studies and in one study after once daily treatment. In the supportive study, patients demonstrated a statistically significant improvement with NASONEX Aqueous nasal spray at a dose of 200 mcg once a day in relief of nasal congestion and reduction of polyp size with 4 months of treatment compared to placebo.

In two trials with 1954 patients 12 years of age and older with signs and symptoms of acute rhinosinusitis for 7 to 28 days prior to baseline, NASONEX Aqueous Nasal Spray 200 µg 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 $p = 0.038$). In P02683, NASONEX Aqueous Nasal Spray 200 µg twice daily reduced the MSS score (averaged across the 15-day treatment period) by 55.6% from baseline, whereas placebo treatment reduced the MSS by 45.6%. In P02692, NASONEX Aqueous

Nasal Spray 200 µg twice daily reduced the MSS score by 48.4% from baseline, whereas placebo treatment reduced the MSS by 41.5% (Table 1).

Table 1 Change from Baseline AM/PM Days 1-15 Major Symptom Score

	Study P02683		Study P02692	
Treatment (n)	MF 200 µg BID (233)	Placebo (247)	MF 200 µg BID (236)	Placebo (242)
Mean score at baseline	8.29	8.36	7.70	7.72
Mean change in score from baseline	-4.51	-3.75	-3.76	-3.36
Mean% change in score from baseline	-55.6%	-45.6%	-48.4%	-41.5%
P-value vs placebo	<0.001		0.038	

Patients were eligible for study entry only if all signs and symptoms suggestive of bacterial rhinosinusitis were absent. These signs and symptoms were: fever >38.3°C; persistent severe unilateral facial pain or tooth pain; orbital or periorbital facial swelling; dental involvement; and worsening of symptoms after initial improvement. In addition, patients with severe symptoms (on a scale of mild, moderate or severe) in more than three of the five MSS symptom groups were not eligible for study participation. Thus, study subjects generally had mild or moderate rhinosinusitis, likely of non-bacterial origin. Consistent with this, 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. Overall, fewer subjects treated with NASONEX Aqueous Nasal Spray 200 µg 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 was low and comparable to the amoxicillin and placebo treatment groups. Treatment duration beyond 15 days was not evaluated in acute rhinosinusitis.

INDICATIONS AND USAGE: NASONEX Aqueous Nasal Spray is indicated for use in adults and children 2 years of age and older to treat the symptoms of seasonal or perennial rhinitis.

In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with NASONEX is recommended two to four weeks prior to the anticipated start of the pollen season.

NASONEX Nasal Spray is also indicated for the treatment of nasal polyps in patients 18 years of age and older. Treatment of nasal polyps in pediatric patients less than 18 years of age has not been established.

NASONEX Nasal Spray is indicated for the treatment of symptoms associated with mild to moderate uncomplicated acute rhinosinusitis in patients 12 years of age and older without signs and symptoms of severe bacterial infection.

DOSAGE AND ADMINISTRATION: After initial priming of the NASONEX Aqueous 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 at least 2 actuations, until a uniform spray is observed, before next use.

Shake container well before each use.
Cleaning: It is important to clean the nasal spray regularly; otherwise it may not work properly. Remove the dust cap and gently pull off the nozzle. Wash the nozzle and dust cap in warm water and then rinse under a running tap. Do not try to unblock the nasal applicator by inserting a pin or other sharp object as this will damage the applicator and cause you not to get the right dose of medicine. Allow to dry in a warm place. Push the nozzle back onto the bottle and replace the dust cap. The spray will need to be re-primed with 2 sprays when first used after cleaning.

Adults (including geriatric patients) and children 12 years of age and older: 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 once daily (total dose 400 micrograms). Dose reduction is recommended following control of symptoms.

Clinically significant onset of action occurs as early as 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 once daily (total daily dose of 200 mcg). If symptoms are inadequately controlled, the dose may be increased to a daily dose of two sprays in each nostril twice daily (total daily dose of 400 mcg). Dose reduction is recommended following control of symptoms.

Acute Rhinosinusitis: The usual recommended dose for acute rhinosinusitis is two sprays (50 micrograms/spray) in each nostril twice daily (total daily dose of 400 mcg). If no improvement is seen after 15 days of twice daily administration, alternative therapies should be considered. If symptoms worsen during treatment, the patients should be advised to consult their physician.

DRUG INTERACTIONS: NASONEX Aqueous Nasal Spray has been administered concomitantly with loratadine with no apparent 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.

ADVERSE EFFECTS:

Clinical Trials Experience

Treatment-related local adverse events reported in clinical studies include headache (8%), epistaxis (i.e., frank bleeding, blood-tinged mucus, and blood flecks) (8%), pharyngitis (4%), nasal burning (2%), nasal irritation (2%), and nasal ulceration, 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 active control nasal corticosteroids studied (up to 15%). The incidence of all other effects was comparable with that of placebo.

In the pediatric population, the incidence of adverse effects, e.g., headache (3%), epistaxis (6%), nasal irritation (2%) and sneezing (2%) was comparable to placebo.

Post-Marketing Experience

Rarely, immediate hypersensitivity reactions (e.g., bronchospasm, dyspnea) may occur after intranasal administration of mometasone furoate monohydrate. Very rarely, anaphylaxis, angioedema, chest pain, palpitation and tachycardia have been reported.

Disturbances of taste and smell have been reported very rarely.

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.

Acute Rhinosinusitis

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.

Treatment related adverse events reported most frequently in NASONEX 200 µg twice daily group include epistaxis (3.7% vs. placebo 2.6%), diarrhoea (2.1% vs. placebo 0.8%), headache (1.7% vs. placebo 2.4%), nausea (1.7% vs. placebo 0.6%) and abdominal pain (1.7% vs. placebo 1.0%).

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

CONTRAINDICATIONS: Hypersensitivity to any ingredients of NASONEX Aqueous Nasal Spray.

PRECAUTIONS: NASONEX Aqueous Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

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.

Following 12 months of treatment with NASONEX Aqueous Nasal Spray, 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 Aqueous Nasal Spray over several months or longer should be examined periodically for possible

changes in the nasal mucosa. If localized fungal infection of the nose or pharynx develops, discontinuance of NASONEX Aqueous Nasal Spray therapy or appropriate treatment may be required. Persistence of nasopharyngeal irritation may be an indication for discontinuing NASONEX Aqueous Nasal Spray.

NASONEX Aqueous Nasal Spray 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.

There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX Aqueous Nasal Spray. However, patients who are transferred from long-term administration of systemically active corticosteroids to NASONEX Aqueous Nasal Spray require careful attention. Systemic corticosteroid withdrawal in such patients may result in adrenal insufficiency for a number of months until recovery of HA axis function. If these patients exhibit signs and symptoms of adrenal insufficiency, systemic corticosteroid administration should be resumed and other modes of therapy and appropriate measures instituted.

During transfer from systemic corticosteroids to NASONEX Aqueous Nasal Spray, some patients may experience symptoms of withdrawal from systemically active corticosteroids (e.g., joint and/or muscular pain, lassitude, and depression initially) despite relief from nasal symptoms and will require encouragement to continue NASONEX Aqueous Nasal Spray therapy. Such transfer may also unmask pre-existing allergic conditions such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

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 aerosolized corticosteroids, instances of nasal septum perforation or increased intraocular pressure have been reported very rarely.

General Nasal Corticosteroid Warning: Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Growth retardation has been reported in children receiving 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 patient to a paediatric specialist.

Treatment with higher than recommended doses 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 a placebo-controlled clinical trial in which paediatric patients were administered NASONEX 100 micrograms daily for one year, no reduction in growth velocity was observed.

Nasal and inhaled corticosteroids have been associated with the development of glaucoma and/or cataracts. Therefore, close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

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.

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

Use in Acute Rhinosinusitis

If signs and symptoms of severe bacterial infection are observed (such as fever, persistent severe unilateral facial/tooth pain, orbital or periorbital facial swelling, or worsening of symptoms after an initial improvement), the patient should be advised to consult their physician immediately. If these signs and symptoms are present at the time of diagnosis, treatment with NASONEX should not be initiated.

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

USAGE DURING PREGNANCY AND LACTATION: There are no adequate or well controlled studies in pregnant women.
As with other nasal corticosteroid preparations, NASONEX Aqueous Nasal Spray should be used in pregnant women, nursing mothers or women of childbearing age only if 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.

OVERDOSAGE:
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 MFNS, overdose is unlikely to require any therapy other than observation.

Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of hypopituitary-adrenal (HPA) axis function.

HOW SUPPLIED: Each unit of NASONEX Aqueous Nasal Spray delivers 60 sprays or 140 sprays; containing 50 micrograms mometasone furoate per actuation.

Shelf-life information can be found on the immediate and outer labels of the product.

STORAGE: Store below 30°C. Store away from heat. Do not freeze. Keep out of reach of children.

Further information can be obtained from the doctor or pharmacist.

Product Registrant:
Organon Singapore Pte. Ltd.
150 Beach Road
#36-01/08 Gateway West
Singapore 189720

Zuellig Pharma (B) Sdn Bhd
Unit 5, 1st floor,
Spg 607, Jalan Gadong,
Kg Beribi, BSB, BE1118
Brunei Darussalam

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