NASONEX® Aqueous Nasal Spray LPC-OG0887-NS-082017

Brand of mometasone furoate monohydrate

FOR INTRANASAL ADMINISTRATION

DESCRIPTION: NASONEX Aqueous Nasal Spray is a 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 13 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 UDS assay in rat hepatocytes, 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 oral, topical (dermal) and/or subcutaneous routes. Umbilical hernia occurred in rats administered $\geq$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 $\geq$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 the exaggerated pharmacologic effects of glucocorticoids.

The carcinogenicity potential of inhaled mometasone furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25 to 2.0 micrograms/l was investigated in 24-month studies in mice and rats. 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.

CLINICAL PHARMACOLOGY: Pharmacokinetic properties: 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 mostly as metabolites in the bile and to a limited extent in the urine.

Pharmacodynamic properties: 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 eosinophil activity and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins.

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

INDICATIONS AND USAGE: NASONEX Aqueous Nasal Spray is indicated for use in adults, adolescents and children between the ages of 3 and 11 years 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.

NASONEX Aqueous Nasal Spray is indicated for the treatment of symptoms associated with acute rhinosinusitis in patients 12 years of age and older without signs or 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 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 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 3 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.

Acute Rhinosinusitis: Adults (including geriatric patients) and adolescents 12 years of age or older: The usual recommended dose for acute rhinosinusitis is two actuations (50 micrograms/actuation) in each nostril twice daily (total daily dose of 400 micrograms). If no improvement is seen after 15 days of twice daily administration, alternative therapies should be considered. If symptoms worsen during treatment, the patient 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

Seasonal allergic or perennial rhinitis: Treatment-related local adverse events reported in clinical studies in adult patients and adolescents 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 (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 corticoids 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 (4%).

Rarely, immediate hypersensitivity reactions (e.g. bronchospasm, dyspnea) may occur after intranasal administration of mometasone furoate monohydrate. Very rarely, anaphylaxis and angioedema 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.

Post-Market Experience

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; severe nasal infection especially candidiasis; persons with hemorrhagic diathesis or with a history of recurrent nasal bleeding.

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 HPA 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.

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 pediatric patients were administered NASONEX 100 micrograms daily for one year, no reduction in growth velocity was observed.

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.

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.

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.

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 Aqueous Nasal Spray for the treatment of symptoms of rhinosinusitis in children under 12 years of age have not been studied. *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.

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 of NASONEX is <1% (using a sensitive assay with a lower quantitation limit of 0.25 pg/ml), overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage.

HOW SUPPLIED: Each unit of NASONEX Aqueous Nasal Spray delivers 40 sprays or 60 sprays or 120 sprays or 140 sprays; containing 50 micrograms mometasone furoate per actuation.

Not all pack sizes may be marketed.

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

STORAGE: Store in a cool place, 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.

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