NASONEX® Aqueous Nasal Spray
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 µg mometasone furoate.

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, anti-androgenic, estrogenic or anti-estrogenic activity but, like other glucocorticoids, it possesses 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.

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 µg/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 pro-allergic cytokines IL-4 and IL-5.

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 leukocytes of allergic patients. In addition, it is an extremely potent inhibitor of the production of the Th2 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 i*n 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 µg/kg (2.6 times the human dose by inhalation). At 15 µg/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 µg/kg dermally, cleft palate in mice administered 180 µg/kg subcutaneously, and gall-bladder agenesis, umbilical hernia, and flexed front paws in rabbits administered ≥150 µg/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 negligible (≤0.1%) systemic bioavailability and is generally undetectable in plasma, despite the use of a sensitive assay with a lower quantitation limit of 50 pg/ml; thus, there are no relevant pharmacokinetic data for this dosage form. 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 eosinophil activity and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins.

Indications and Usage:
NASONEX® Aqueous Nasal Spray is indicated for use in adults and children **3** years of age and older to treat the symptoms of allergic seasonal or allergic perennial rhinitis.
In patients 12 years and older who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with NASONEX® Aqueous Nasal Spray is recommended two to four weeks prior to the anticipated start of the pollen season.

Dosage and Administration:
After initial priming of the NASONEX® Aqueous Nasal pump (usually 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 µg 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.

The bottle should be discarded after 120 actuations or within 2 months of first use.

Adults (including geriatric patients) and children 12 years of age and older:
The usual recommended dose for treatment is two sprays (50 µg/spray) in each nostril once daily (total dose 200 µg). Once symptoms are controlled, dose reduction to one spray in each nostril (total dose 100 mg) may be effective for maintenance.

If symptoms are inadequately controlled, the dose may be increased to four sprays in each nostril (total 400 µg). Dose reduction is recommended following control of symptoms.

Children 3 to 11 years of age*:*
The usual recommended dose for treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis is 1 spray (50 µg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 100 µg).
Administration to young children should be aided by an adult.
Clinically significant onset of action occurs as early as 12 hours after the first dose.

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. Mometasone furoate plasma concentrations were not detectable. The combination therapy was well tolerated.

Adverse Effects:
Treatment-related local adverse events reported in clinical studies include headache (8%), epistaxis (i.e., frank bleeding, blood-tinged mucous, 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 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.

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 test and smell have been reported very rarely.

Contraindications:
Hypersensitivity to any ingredients of NASONEX® Aqueous Nasal Spray.
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.

Special Warnings and Precautions for Use:
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.

Although NASONEX® Aqueous Nasal Spray will control the nasal symptoms in most patients, the concomitant use of antihistamines may provide additional relief of other symptoms, particularly ocular symptoms.

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 hypothalmic-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.

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.

Full benefit of treatment may not be achieved in the first 48 hours.

In a placebo-controlled clinical trial in which pediatric patients were administered NASONEX® Aqueous Nasal Spray 100 µg daily for one year, no reduction in growth velocity was observed.

The potential of NASONEX® Aqueous Nasal Spray to cause growth suppression in susceptible patients or when given at high doses cannot be ruled out.

Usage During Pregnancy and Lactation:
There are no adequate or well controlled studies in pregnant women. Following intranasal administration of the maximal recommended clinical dose to patients, mometasone plasma concentrations are not measurable; thus fetal exposure is expected to be negligible and the potential for reproductive toxicity, very low.

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 of the negligible (≤0.1%) systemic bioavailability of NASONEX® Aqueous Nasal Spray, overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage. Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function.

Storage:
Do not freeze. Keep away from heat.
Store in a cool place between 2º and 25ºC.

Manufacturer:
Schering-Plough Laboratories N.V., Belgium
a wholly owned subsidiary of Schering-Plough Corporation, U.S.A.

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