# PRODUCT MONOGRAPH

# NASONEX ALLERGY AND CONGESTION

mometasone furoate monohydrate nasal spray

50 mcg/metered spray
(as mometasone furoate)

## Corticosteroid

**Schering-Plough Canada Inc.**
Kirkland, Québec
H9H 4M7

Date of Preparation:
July 14, 1998

Date of Revision:
June 19, 2014

Submission Control No. 170095

## Table of Contents

**NASONEX ALLERGY AND CONGESTION**
(mometasone furoate monohydrate nasal spray)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Nonmedicinal Ingredients |
|---|---|---|
| nasal | suspension / 50 mcg per metered spray | benzalkonium chloride, citric acid, dispersible cellulose BP 65 cps (carboxymethylcellulose sodium, microcrystalline cellulose), glycerol, Polysorbate 80, purified water, and sodium citrate dihydrate |

### INDICATIONS AND CLINICAL USE
NASONEX ALLERGY AND CONGESTION (mometasone furoate monohydrate nasal spray) is indicated for use in adults and children of 12 years and older to treat the symptoms of seasonal or perennial allergic rhinitis.

Full effect depends on continued use. Therefore, regular usage is essential since symptoms relief may be obtained only after 12 to 48 hours of treatment.

### CONTRAINDICATIONS
Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

NASONEX ALLERGY AND CONGESTION 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.

### WARNINGS AND PRECAUTIONS

**General**
During transfer from systemic corticosteroid to NASONEX ALLERGY AND CONGESTION, 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 ALLERGY AND CONGESTION therapy. Such transfer may also unmask pre-existing allergic conditions such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

**Ear/Nose/Throat**
NASONEX ALLERGY AND CONGESTION 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 NASONEX ALLERGY AND CONGESTION, 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 ALLERGY AND CONGESTION 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 ALLERGY AND CONGESTION or appropriate treatment may be required. Persistence of nasopharyngeal irritation may be an indication for discontinuing NASONEX ALLERGY AND CONGESTION.

Following the use of intranasal aerosolized corticosteroids, instances of nasal septum perforation have been reported very rarely.

**Endocrine and Metabolism**
There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged (12 months) treatment with NASONEX ALLERGY AND CONGESTION. However, patients who are transferred from long-term administration of systemically active corticosteroids to NASONEX ALLERGY AND CONGESTION 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.

Although this has not been observed with NASONEX ALLERGY AND CONGESTION, when intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects may occur, such as hypercorticism, suppression of HPA function and/or reduction of growth velocity in children or teenagers. Children should be maintained on the lowest dose which delivers adequate symptom control.

**Immune**
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.

**Ophthalmologic**
Following the use of intranasal aerosolized corticosteroids, instances of increased intraocular pressure have been reported very rarely.

Although not observed with NASONEX ALLERGY AND CONGESTION, glaucoma and/or cataracts have been reported in patients receiving other intranasal corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

**Special Populations**

***Pregnancy and Nursing Mothers***
There are no adequate or well-controlled studies in pregnant or nursing women.

As with other nasal corticosteroid preparations, NASONEX ALLERGY AND CONGESTION 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.

***Pediatrics***
NASONEX ALLERGY AND CONGESTION permitted normal growth in a placebo-controlled clinical trial in which pediatric patients were administered NASONEX ALLERGY AND CONGESTION spray 100 mcg daily for one year.

Although not observed with NASONEX ALLERGY AND CONGESTION, other intranasal corticosteroids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticosteroids appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

The potential of NASONEX ALLERGY AND CONGESTION Nasal Spray 50 mcg to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

## ADVERSE REACTIONS

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.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

### *Allergic Rhinitis*

Adults and adolescents ≥12 years of age: Table 1 demonstrates the incidence of treatment related adverse reactions associated with NASONEX ALLERGY AND CONGESTION based upon the pooled data from clinical trials.

**Table 1: Treatment related adverse reactions occurring at an incidence of ≥1% and more commonly than placebo**

| **Adverse Reactions** | NASONEX ALLERGY AND CONGESTION * **n = 3210 n (%)** | **Placebo n = 1671 n (%)** |
|---|---|---|
| Headache | 265 (8) | 101 (6) |
| Epistaxis | 267 (8) | 89 (5) |
| Pharyngitis | 124 (4) | 58 (3) |

* 50 mcg to 800 mcg of mometasone furoate daily

Treatment-related local adverse events reported in clinical studies, headache, epistaxis (e.g., frank bleeding, blood-tinged mucus, and blood flecks), pharyngitis, and nasal ulceration are typically observed with use of a corticosteroid nasal spray. In addition, the following adverse events occurred at a frequency equal to or less than placebo, nasal burning (2% vs. 3%) and nasal irritation (2% vs. 2%), respectively.

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%). The incidence of all other effects was comparable with that of placebo.

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**
The following additional treatment related adverse reactions occurred in clinical trials in patients using NASONEX ALLERGY AND CONGESTION with an incidence of <1% and occurred at a greater incidence than placebo*:

*Blood and lymphatic system disorders:* lymphadenopathy
*Cardiac disorders:* palpitation, tachycardia
*Eye disorders:* lacrimation, conjunctivitis, dry eyes, abnormal vision
*Ear and labyrinth disorders:* earache, tinnitus
*Gastrointestinal disorders:* abdominal pain, constipation, diarrhea, gastritis, nausea, tongue disorder, tooth disorder
*General disorders and administration site conditions:* dry mouth, allergy aggravated, chest pain, edema, face edema, fever, influenza like symptoms, thirst, taste perversion
*Infections and infestations:* cold sore non herpetic, infection, bacterial infection
*Investigations:* hepatic enzymes increased
*Musculoskeletal and connective tissue disorders:* arthralgia, myalgia
*Nervous system disorders:* tremor, vertigo, migraine
*Psychiatric disorders:* depression, paranoia, somnolence
*Respiratory, thoracic and mediastinal disorders:* dysphonia, bronchitis, dyspnea, laryngitis, nasal septum ulceration, sinusitis, wheezing
*Skin and subcutaneous tissue disorders:* acne, dermatitis, erythematous rash

*Vascular disorders:* hypertension
*Events reported by more than 1 patient

**Post-Market Adverse Drug Reactions**
The following adverse reactions have been identified during the post-marketing period for NASONEX ALLERGY AND CONGESTION: anaphylaxis and angioedema, disturbances in smell and nasal septal perforation. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

## DRUG INTERACTIONS

**Drug-Drug Interactions**
NASONEX ALLERGY AND CONGESTION 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.

Inhibitors of Cytochrome P450 3A4: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. *In vitro* studies have confirmed the primary role of cytochrome CYP 3A4 in the metabolism of this compound. Coadministration with ketoconazole, a potent CYP 3A4 inhibitor, may increase the plasma concentrations of mometasone furoate.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**
The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. Since the effect of NASONEX ALLERGY AND CONGESTION depends on its regular use, patients should be instructed to take the nasal inhalation at regular intervals and not, as with other nasal sprays, as they feel necessary.

In the presence of excessive nasal mucous secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases, it is advisable to use a nasal vasoconstrictor for 2 to 3 days prior to starting treatment with NASONEX ALLERGY AND CONGESTION.

**Recommended Dose and Dosage Adjustment**

***Treatment of seasonal or perennial allergic rhinitis:***

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

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

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

**Administration**
Each actuation delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent up to 50 mcg mometasone furoate. Prior to administration, NASONEX ALLERGY AND CONGESTION nasal pump should be primed by actuating the pump 10 times (until a uniform spray is observed). 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.

Patients should be instructed on the correct method of use, which is to blow the nose, then insert the nozzle carefully into the nostril, compress the opposite nostril and actuate the spray while inspiring through the nose, with the mouth closed.

## 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 NASONEX ALLERGY AND CONGESTION, overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage.

| For management of suspected drug overdose, contact your regional Poison Control Centre. |
|---|

## ACTION AND CLINICAL PHARMACOLOGY

**Mechanism of Action**
Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are minimally systemically active.

**Pharmacodynamics**
In two clinical studies utilizing nasal antigen challenge, NASONEX ALLERGY AND CONGESTION 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. The clinical significance of these finding is not known.

Two Phase I studies conducted to assess the systemic exposure and tolerability of NASONEX ALLERGY AND CONGESTION in children aged 3 to 12 years showed no clinically relevant systemic exposure to NASONEX ALLERGY AND CONGESTION and indicated that

NASONEX ALLERGY AND CONGESTION was well tolerated. A third Phase I study in children aged 6 to 12 years showed normal short-term lower leg growth velocity.

The results of Phase II and Phase III studies indicated no evidence of HPA (hypothalamic-pituitary-adrenal) axis suppression following treatment with NASONEX ALLERGY AND CONGESTION and demonstrated that NASONEX ALLERGY AND CONGESTION can alleviate the allergic symptoms in pediatric patients aged 3 to 12 years with seasonal and perennial allergic rhinitis.

**Pharmacokinetics**

***Absorption:***

Mometasone furoate monohydrate, 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.

***Distribution:***

The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.

***Metabolism:***

Studies have shown that any portion of a mometasone furoate dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon *in vitro* incubation, one of the minor metabolites formed is 6ß-hydroxymometasonefuroate. In human liver microsomes, the formation of the metabolite is regulated by cytochrome P-450 3A4 (CYP3A4).

***Elimination:***

Following intravenous administration, the effective plasma elimination half-life of mometasone furoate is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

## STORAGE AND STABILITY

NASONEX ALLERGY AND CONGESTION should be stored between 2° and 25°C and protected from light. Do not freeze.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### *Dosage Forms*
NASONEX ALLERGY AND CONGESTION is formulated as an aqueous nasal suspension for nasal administration via a metered-dose manual pump spray delivering 140 doses of 50 mcg mometasone furoate. NASONEX ALLERGY AND CONGESTION is also available as a sample and trade sizes containing 60 doses of 50 mcg mometasone furoate.

### *Composition*
Each actuation delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent to 50 mcg mometasone furoate.

The nonmedicinal ingredients include benzalkonium chloride, citric acid, dispersible cellulose BP 65 cps (carboxymethylcellulose sodium, microcrystalline cellulose), glycerol, Polysorbate 80, purified water, and sodium citrate dihydrate.

### *Packaging*
NASONEX ALLERGY AND CONGESTION is supplied in a single pack (1 bottle) or a dual pack (2 bottles). Sample and trade sizes (60 doses) are also available.

# PART II: SCIENTIFIC INFORMATION

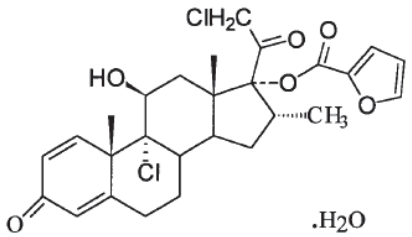
## PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Mometasone furoate monohydrate

Chemical Name: 9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione monohydrate

Structural Formula:




Molecular Formula: $C_{27}H_{30}Cl_2O_6 \cdot H_2O$

Molecular Weight: 539.45

**Description:**

Physical form: White to off-white powder

Solubility: Mometasone furoate monohydrate is practically insoluble in water (0.02 mg/mL). It is slightly soluble (4–8 mg/mL) in methanol, ethanol, and isopropanol. It is soluble (59–74 mg/mL) in acetone and chloroform, and freely soluble (>100 mg/mL) in tetrahydrofuran.

## CLINICAL TRIALS

### *Treatment of allergic rhinitis*

### *Seasonal allergic rhinitis in adolescents and adults*

The safety and efficacy of NASONEX ALLERGY AND CONGESTION in the treatment of patients with seasonal allergic rhinitis (aged 12 years and over) was investigated in six clinical trials. Altogether, these trials enrolled a total of 2544 patients of whom 718 were randomized to treatment with NASONEX ALLERGY AND CONGESTION 200 mcg once daily.

The results of three phase III clinical trials (14- or 28-day studies) with a total of 788 patients who received NASONEX ALLERGY AND CONGESTION or placebo and evaluated for efficacy are presented in Table 2. The primary efficacy endpoint was the change from baseline in Physician-Evaluated Total Nasal Symptom Score (TNSS) after one week of therapy in Study I92-200. In studies C93-013 and I94-001, the primary efficacy endpoint was the change from baseline in Patient-Evaluated Total Nasal Symptom Score over Days 1–15.

**Table 2: Effect of Mometasone furoate monohydrate nasal spray in Phase III, Randomized, Placebo-Controlled Trials in patients with SAR**

| | NASONEX ALLERGY AND CONGESTION **100 mcg OD** | | NASONEX ALLERGY AND CONGESTION **200 mcg OD** | | **Placebo** | |
|---|---|---|---|---|---|---|
| | **N** | **Mean** | **N** | **Mean** | **N** | **Mean** |
| **Study I92-200** | | | | | | |
| **TNSS**[1] – Baseline | 122 | 8.1 | 122 | 8.1 | 110 | 8.0 |
| **TNSS**[1] – Change from Baseline to Day 8 (%)[3] | 120 | -4.3* (-53%) | 120 | -4.7* (-59%) | 106 | -2.6 (-34%) |
| **Study C93-013** | | | | | | |
| **TNSS**[2] – Baseline | | | 111 | 7.6 | 116 | 7.6 |
| **TNSS**[2] – Change from Baseline over Days 1–15 (%)[3] | | | 111 | -2.3* (-25%) | 116 | -1.5 (-17%) |
| **Study I94-001** | | | | | | |
| **TNSS**[2] – Baseline | | | 104 | 7.4 | 103 | 7.3 |
| **TNSS**[2] – Change from Baseline over Days 1–15 (%)[3] | | | 104 | -2.8* (-35%) | 103 | -0.9 (-10%) |

* $P < 0.01$ vs. placebo.

[1] Physician-Evaluated Total Nasal Symptom Score (TNSS). Total of individual nasal symptoms combined (rhinorrhea, nasal stuffiness/congestion, nasal itching and sneezing). Symptoms were scored according to the following rating system; 0 = none, 1 = mild, 2 = moderate, 3 = severe.

[2] Patient-Evaluated Total Nasal Symptom Score (TNSS). Total of individual nasal symptoms combined (rhinorrhea, nasal stuffiness/congestion, nasal itching and sneezing). Symptoms were scored according to the following rating system; 0 = none, 1 = mild, 2 = moderate, 3 = severe.

[3] Percent change is the difference between post treatment mean score and baseline mean score divided by Baseline mean score, multiplied by 100.

***Perennial allergic rhinitis in adolescents and adults***

The safety and efficacy of NASONEX ALLERGY AND CONGESTION in the treatment of patients (aged 12 and over) with perennial allergic rhinitis (PAR) was investigated in three phase III clinical trials of 12-week duration in 875 patients who received NASONEX ALLERGY AND CONGESTION or placebo and evaluated for efficacy.

The primary efficacy endpoint was the change from baseline in Patient-Evaluated Total Nasal Symptom Score (TNSS) from Days 1 to 15. Results of these studies are presented in Table 3.

**Table 3: Patient-Evaluated Total Nasal Symptom Score[1] (TNSS) Results of Trials in Patients with PAR**

| **Primary Endpoint(s)** | | | | |
|---|---|---|---|---|
| | NASONEX ALLERGY AND CONGESTION **200 mcg OD** | | **Placebo** | |
| | **N** | **Mean** | **N** | **Mean** |
| **Study C92-280** | | | | |
| Baseline | 160 | 6.6 | 160 | 6.9 |
| Change from baseline over Days 1–15 (%)[2] | 160 | -1.5* (-21%) | 158 | -1.0 (-13%) |
| **Study I92-293** | | | | |
| Baseline | 129 | 6.3 | 124 | 6.2 |
| Change from baseline over Days 1–15 (%)[2] | 127 | -1.7* (-25%) | 121 | -1.2 (-15%) |
| **Study I94-079** | | | | |
| Baseline | 154 | 6.1 | 148 | 6.0 |
| Change from baseline over Days 1–15 (%)[2] | 154 | -2.2** (-37%) | 148 | -1.3 (-22%) |

* P = 0.01 vs. placebo; ** P < 0.01 vs. placebo.

[1] Total of individual nasal symptoms combined (rhinorrhea, nasal stuffiness, nasal itching and sneezing). Symptoms were scored according to the following rating system; 0 = none, 1 = mild, 2 = moderate, 3 = severe.

[2] Percent change is the difference between post treatment mean score and baseline mean score divided by Baseline mean score, multiplied by 100.

## DETAILED PHARMACOLOGY

### Animal

***Pharmacodynamics***

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 TNFa. Mometasone furoate ($IC_{50}$ = 0.12 nM) was also at least six times more potent than BDP and betamethasone at inhibiting IL-5 production.

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 mcg/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.

Mometasone furoate is devoid of androgenic, antiandrogenic, estrogenic or antiestrogenic activity but, like other glucocorticosteroids, it exhibits 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 general pharmacodynamic activity studies, mometasone furoate did not show mineralocorticoid activity. MF did not exert prominent effects on the central or autonomic nervous system. No significant effect was seen on blood pressure, heart rate, or ECG recordings. Mometasone furoate did not alter secretion of gastric acid, pepsin or bile. Mometasone furoate increased urine volume and potassium secretion only at very high doses given subcutaneously. No effect was seen on basic respiratory function. These results suggest no particular adverse effect or class of effects associated with administration of mometasone furoate.

***Pharmacokinetics***

The intranasal administration of mometasone furoate suspension resulted in either very low / dose-proportional / gender independent or nonquantifiable plasma drug concentrations. Similar results were seen for total radioactivity upon intranasal dosing with radiolabeled drug.

By comparison with the AUC following IV dosing, the absolute bioavailability of MF following intranasal administration was less than 1% in rats and dogs, and following PO (suspension) administration was 1.4% in rats and 1.7% in mice. In dogs, plasma drug concentrations were generally not quantifiable following PO administration of the MF suspension. The pharmacokinetics of mometasone furoate in the mouse, rat and especially dog, were quite comparable to those obtained in humans.

**Human**

***Pharmacology***

Mometasone furoate significantly inhibits the release of leukotrienes from leukocytes of allergic patients. In addition, it is an inhibitor of the production of the $Th_2$ cytokines, IL-4 and IL-5, from human CD4+ T-cells.

In two clinical studies using nasal antigen challenge, mometasone aqueous nasal spray has shown anti-inflammatory activity in both the early and late phase allergic responses. This has been demonstrated by decreases (versus placebo) in histamine and eosinophil activity and reductions (versus baseline) in eosinophils, neutrophils and epithelial cell adhesion proteins. The clinical significance of these findings is not known.

In patients with seasonal allergic rhinitis NASONEX ALLERGY AND CONGESTION demonstrated a clinically significant onset of action within 12 hours of the first dose.

In children, results from plasma samples assayed for NASONEX ALLERGY AND CONGESTION from one clinical study (Phase III) and two multiple-dose Phase I studies confirmed the general absence of systemic plasma concentrations following intranasal administration of NASONEX ALLERGY AND CONGESTION.

***Pharmacokinetics***
Mometasone furoate, 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 absorbed undergoes extensive first-pass hepatic metabolism prior to excretion in urine and bile.

## TOXICOLOGY

In a series of studies designed to maximize exposure to mometasone furoate, there was no unique or special finding regardless of route of administration or formulation. In single- and multiple-dose toxicology studies and in reproductive toxicity studies, all findings were typical glucocorticoid class effects and obeyed the well-established dose-response and dose-duration relationships for systemic pharmacologic effects of glucocorticoids. Difficult and prolonged parturition observed in Segment I and Segment III reproduction studies may be related to the progestational effect of mometasone furoate. Reductions in maternal weight gain, fetal weight, and offspring viability, and the occurrence of typical malformations and skeletal variations (reduced ossification) were glucocorticoid class effects.

Based on results of multiple mutagenicity studies and of two carcinogenicity studies, one each in mice and rats, mometasone furoate should not pose a genetic hazard or increase the risk of cancer to patients exposed in a clinical setting. In particular, there was no statistically significant dose-response relationship for any tumour type in either the mouse or rat carcinogenicity study. In the study with mice, an apparent increase in mesenchymal tumours of the bladder and seminal vesicles was considered to have no relevance to assessment of human risk because it is a species- and strain-specific finding without a human correlate. An apparent increase in incidence of pancreatic cell hyperplasia in mid- and high-dose groups (1.0 and 2.0 mcg/L, respectively), and islet cell neoplasia in the high-dose group of male rats was attributed to the well-established metabolic effects of prolonged administration of glucocorticoids (increased glucose and/or insulin resistance). Increases in the incidence of tumours of islet cells are induced by other steroids, and reflect a non-genotoxic mechanism in a species with unique endocrinologic sensitivity.

***Acute Toxicity***
Two acute inhalation toxicity studies were conducted in mice (i.e., 4-hr whole-body exposure to micronized, pure, mometasone furoate powder). In the first study, the mean estimated doses were 582 mg/kg (in mice) and 394 mg/kg (for rats), assuming 100% deposition. No clinical signs were observed in either species during the 36-day post-exposure observation period. However, lower body weights compared to pre-treatment values were observed in both species. In the second study, rats were exposed by whole body exposure to 0.68 mg/L micronized mometasone furoate powder for 4 hours, and then observed for 3 weeks. Weight loss occurred during the observation period; while rales, ano-genital staining, soft stools and emaciation were the principal clinical observations. At necropsy, several rats had discoloured lungs, small spleens and discoloured brown skin.

***Multiple-Dose Toxicity***
The intranasal irritation potential of mometasone furoate aqueous nasal suspensions were assessed in beagle dogs administered daily doses of up to 4.0 mg/dog for three days, one week or one month. The aqueous nasal suspensions did not induce irritation in the nasal mucosa, and no compound-related changes were observed after one month of administration.

Mometasone furoate aqueous nasal suspension was well tolerated in toxicity studies conducted in rats and dogs for 6 months. Rats received doses of up to 0.600 mg/kg (0.18 mg/day; 70 times the proposed human dose); dogs received doses of up to 0.15 mg/kg (2.0 mg/day; 35 times the proposed human dose). Rats treated with 0.6 mg/kg experienced hair loss on the back during the last 5 weeks, which correlated with hypotrichosis. The no-effect dose for pharmacologic effects in rats was 0.050 mg/kg based on low body weight gains at higher doses. Dogs treated with 0.15 mg/kg demonstrated eosinophil counts, which were lower than pre-test and concurrent controls after 4, 13 and 26 weeks. In addition, ACTH response in the 0.045 and 0.15 mg/kg dose groups was lower than control. These differences were dose-related and were attributed to mometasone furoate. No evidence of nasal irritation was present at any dose in either the rat or the dog study. No target organs of systemic toxicity were identified in either study.

Mometasone furoate aqueous nasal spray was well tolerated when administered intranasally to dogs for one year at doses of up to 2.0 mg/day. In the 2.0 mg/day dose group, an increased incidence of alopecia, minimal decreases in lymphocytes and eosinophils, decreases in basal and post-ACTH cortisol response, lower adrenal gland weights, small or atrophied adrenal glands, epidermal atrophy, minimal splenic lymphoid atrophy, minimal focal epithelial attenuation in the nasal turbinates and retained luminal mucus were observed. Dogs treated with ≥0.2 mg/day demonstrated a dose-related increase in smaller or absent lymphoid aggregates. With the exception of minimally increased retained luminal mucus in the 2.0 mg/day dose group, there was no evidence of irritation or inflammation in the nasal turbinates of mometasone furoate-treated dogs. Thus, the changes in the lymphoid aggregates were considered a localized corticosteroid response associated with application and were not considered to be of toxicologic significance.

***Mutagenicity***
Mometasone furoate was nonmutagenic in the mouse lymphoma assay and the salmonella/mammalian microsome mutagenicity 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 and 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.

***Carcinogenicity***
The carcinogenicity potential of inhaled mometasone furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25 to 2.0 mcg/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 tumour types. The apparent increase in mouse bladder/seminal vesicle mesenchymal tumours is considered to have no relevance in human carcinogenic risk assessment since it is a species- and strain-specific finding with no human correlate. The greater incidence of pancreatic islet cell hyperplasia in male rats who received 1.0 and 2.0 mcg/L is attributed to the well-established metabolic effects (increased glucose and/or insulin resistance) following prolonged administration of glucocorticoids. Increases in pancreatic islet cell tumours, which are induced by other steroids, reflects a non-genotoxic mechanism operative in an endocrinologically uniquely sensitively species.

***Reproductive Toxicology***
In subcutaneous Segment I and III studies, mometasone furoate was well tolerated at doses up to 7.5 mcg/kg (2.6 times the human dose by inhalation). At 15 mcg/kg, prolonged gestation and prolonged and difficult labour occurred with a reduction in offspring survival and body weight gain 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 ≥ 600 mcg/kg dermally, cleft palate in mice administered 180 mcg/kg subcutaneously, and gallbladder agenesis, umbilical hernia, and flexed front paws in rabbits administered ≥ 150 mcg/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.

## REFERENCES


1. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (NASONEX®) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy 1996;51:569-576.

2. Drouin M, Yang WH, Bertrand B et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol 1996;77:153-160.

3. Brannan MD, Herron JM, Affrime MB. Safety and tolerability of once daily mometasone furoate aqueous nasal spray in children. Clin Ther 1997;19:1330-1339.

4. Davies RJ, Nelson HS. Once-Daily mometasone furoate nasal spray: Efficacy and Safety of a New intranasal glucocorticoid for allergic rhinitis. Clinical Therapeutic, Vol 19, No. 1, 1997.

5. Mandl M., Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (NASONEX®) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. Annals of Allergy, asthma & Immunology, Oct 1997, pp. 370-378.

6. Minshall E, Graffar O, Cameron L et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (NASONEX®) in the treatment of perennial rhinitis. Otolaryngology-head and neck surgery, Volume 118, Number 5, pp. 648-654.

7. Stjärne P, Mösges, R, Jorissen M et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Otolaryngology-head and neck surgery, Volume 132, Feb 2006, pp. 179-185.

8. Small BC, Hernandez J, Reyes A et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol, Volume 116, Number 6, December 2005, pp. 1275-1281.

9. Meltzer E, Bachert C et al. Treating Acute Rhinosinusitis: Comparing Efficacy and safety of mometasone furoate nasal spray, amoxicillin and placebo., J Allergy Clin Immunol, Volume 116, Number 6, December 2005, pp. 1289-1295.

10. P05002. SCH 32088: Evaluation of the Nasal and Sinus Deposition, Nasal Retention Pattern, and Systemic Exposure to Mometasone Furoate After Nasal Inhalation From a NASONEX Nasal Spray and Alternative Formulations/Devices.

**PART III: CONSUMER INFORMATION**

**NASONEX ALLERGY AND CONGESTION**
**Mometasone furoate monohydrate**
**nasal spray**

**This leaflet is part III of a three-part "Product Monograph", published when NASONEX ALLERGY AND CONGESTION was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about NASONEX ALLERGY AND CONGESTION. Please read this leaflet carefully before you start taking NASONEX ALLERGY AND CONGESTION and contact your doctor or pharmacist if you have any questions about the medication.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
NASONEX ALLERGY AND CONGESTION is used in adults and children 12 years of age and older, for temporary relief of symptoms of the following conditions:

***Seasonal allergic rhinitis:*** also called "outdoor allergies" is caused by allergies to grass, trees and ragweed pollen.

***Perennial allergic rhinitis:*** year round/ indoor allergies caused by dust mites, animals and molds.

The allergy symptoms include
- stuffiness/nasal congestion,
- runny nose,
- nose itching
- sneezing.

Full effect depends on daily and continued use as long as allergy triggers remain.

**What it does:**
When sprayed into the nose, it helps reduce inflammation in nasal passages and relieves the allergy symptoms.

In some patients, NASONEX ALLERGY AND CONGESTION may relieve symptoms within 12 hours; others may have to wait at least 48 hours, even if used daily.

**When it should not be used:**
NASONEX ALLERGY AND CONGESTION should not be used:
- if you are allergic to Mometasone furoate monohydrate nasal-spray or to any of its ingredients.
- if you have an infection in the nose (i.e. yellow or green discharge from the nose) that is not being treated.
- if your nose was recently operated on or injured.
- If you have frequent and severe nosebleeds
- if you have been diagnosed with tuberculosis and it is not being treated.*
- if you have untreated fungal, bacterial, or systemic viral infections.*
- if you have a herpes simplex (virus) infection of the eye and it is not being treated.*

* See WARNINGS AND PRECAUTIONS for additional information.

**What the medicinal ingredient is:**
NASONEX ALLERGY AND CONGESTION contains mometasone furoate monohydrate.

**What the nonmedicinal ingredients are:**
*(alphabetical order):* benzalkonium chloride, carboxymethylcellulose sodium, citric acid, glycerol, microcrystalline cellulose, polysorbate 80, purified water, and sodium citrate dihydrate.

**What dosage forms it comes in:**
NASONEX ALLERGY AND CONGESTION comes in a nasal spray device which delivers 60 sprays (sample and trade sizes) or 140 sprays. Each spray delivers an unscented mist, containing the equivalent of 50 mcg* of mometasone furoate.
** Calculated on the anhydrous basis.*

## WARNINGS AND PRECAUTIONS

Do not spray NASONEX ALLERGY AND CONGESTION into your eyes or mouth. It is for use in the nose only.

Before you use NASONEX ALLERGY AND CONGESTION talk to your doctor or pharmacist if you are pregnant or nursing a baby. Breast-feeding is not recommended during treatment with this drug.
If you have any of the following conditions consult your doctor or pharmacist before using NASONEX ALLERGY AND CONGESTION. If you develop one of these conditions while using this drug, stop treatment and see your doctor:
- sores in the nose
- tuberculosis (active or previous)
- infection (fungal, bacterial or viral)
- herpes simplex (virus) infection of the eye
- Change in vision
- Severe or frequent nose bleed

(See **ABOUT THIS MEDICATION- When it should not be used**, for additional information.)

Although not observed with NASONEX ALLERGY AND CONGESTION, development of glaucoma (elevated pressure inside the eye ball) or cataracts (clouding of the lens of the eye) have been reported with other intranasal and inhaled corticosteroids.

Although not observed with NASONEX ALLERGY AND CONGESTION, slower rate of growth has been reported in some children receiving other intranasal corticosteroid. You and your doctor should monitor your child's growth.

Contact your doctor if you think you have developed an infection in the nose after starting NASONEX ALLERGY AND CONGESTION (i.e. normally clear discharge from the nose has turned yellow or green) or if you have, or come into contact with someone who has chickenpox, measles or tuberculosis;

Be sure to use this medicine exactly as instructed. Do not use more NASONEX ALLERGY AND CONGESTION than recommended in an attempt to increase its effectiveness, (See **PROPER USE OF THIS MEDICATION** for additional information.) Do not use this product for treating other disease such as cold.

## INTERACTIONS WITH THIS MEDICATION

To avoid the possibility of drug interactions, be sure to advise your physician or pharmacist of any other medications that you are taking, particularly corticosteroid medicine, either by mouth or by injection.

## *PROPER USE OF THIS MEDICATION*

***FOR INTRANASAL USE ONLY. DO NOT SPRAY INTO EYES or MOUTH***

Follow the INSTRUCTIONS FOR USE described below to properly use this spray bottle
If you have any questions, call 1-866-241-3891

Usual dose and Directions for use
Adults and children 12 years of age and older
Once daily, spray two times into each nostril while sniffing gently.

When your symptoms are under control, you may reduce to one (1) spray into each nostril once daily to maintain control of your symptoms.

You may stop and re-start use as needed based on your symptoms.

**When using this product:**

- Do not use more than 4 sprays in 24 hours;
- Do not share this bottle with anyone else as this may spread germs.
- Do not use continuously for more than six months without consulting your doctor.

Stop use and ask a doctor or pharmacist if

- Your allergy symptoms do not improve after one week.
- Changes to the eyesight
- Severe or frequent nosebleeds
- You have or developed symptom of an infection

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed dose:**

If you miss taking your dose on time, do not worry; take a dose if you remember within an hour or so. However, if you do not remember until later, skip the missed dose and go back to your regular dosing schedule. Do not double the dose.

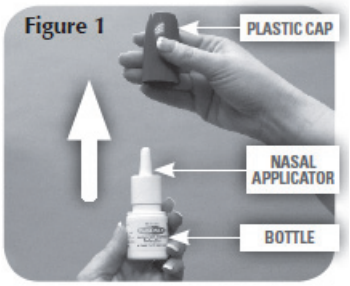
## INSTRUCTIONS FOR USE

### HOW TO PRIME THE PUMP

**1.** Shake the bottle well.

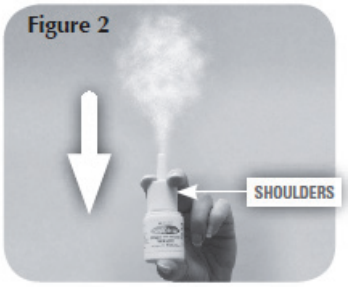
**2.** Remove the plastic cap **(Figure 1)**.

Figure 1




**3.** Prime the pump into the air the first time it is used, or when not used for a week or more.

**Do not pierce the nasal applicator.**
• To prime the pump, press downward on the shoulders of the nasal applicator using your index finger and middle finger while holding the base of the bottle with your thumb **(Figure 2)**. Point the spray away from you while doing this.

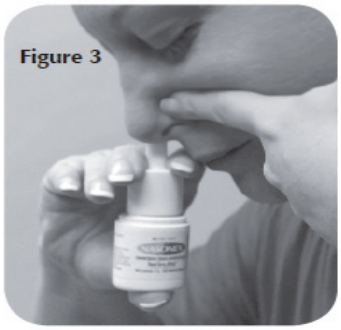



• Press down and release the pump ten times or until a fine spray appears, taking care not to spray into eyes or face.
• The pump is now ready to use.

**HOW TO USE AND CLEAN**

**1.** Shake the bottle well before each use.

**2.** **.** Gently blow your nose to clear the nostrils.
**.** With your finger, hold one nostril shut.
**.** Tilt your head forward slightly, keep the bottle upright, and carefully insert the nasal applicator into the other nostril **(Figure 3)**.




**Do not spray directly onto the nasal septum (the wall between the two nostrils).**

**3.** **.** Hold the spray bottle upright and press firmly downward on the shoulders of the nasal applicator.
**.** Breathe gently inward through the nostril.
**.** Then breathe out through the mouth.
– Adults and children 12 years and over: two sprays in each nostril.

**4.** Repeat in the other nostril.

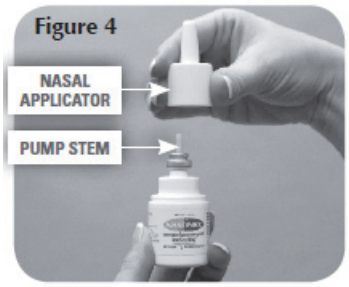
**5.** Wipe the outside of the nasal applicator with a clean tissue and replace the plastic cap after each use.

**WHAT TO DO IF BLOCKED**

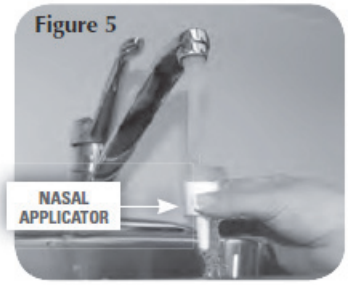
Clean the inside of the applicator if it gets blocked.
**Do not try to unblock the nasal applicator by inserting a pin or other sharp object, as this will damage the applicator.**

**1.** Remove the plastic cap.

**2.** Pull gently upward on the nasal applicator to remove **(Figure 4)**.




**3.** Rinse both ends of the nasal applicator under cold water. Let air dry **(Figure 5)**.




**4.** Once dry, put nasal applicator back on pump stem.

**5.** Reprime the pump.
(See HOW TO PRIME THE PUMP instructions).

Please keep this package insert for future use.
If you have any questions, call 1-866-241-3891

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects that may occur with the use of corticosteroid nasal sprays, including NASONEX ALLERGY AND CONGESTION, are headache, nose-bleed or blood-tinged mucus, burning or irritation inside the nose, sneezing or sore throat.

Disturbances of taste and smell have been reported very rarely. If these side effects do not go away or worsen, stop use and contact your doctor or pharmacist.
The following less common side effects have been seen in Clinical Trials: swollen lymph nodes, vision changes, eye tearing, dry eyes, eye inflammation or infection, ear ache, ringing in the ears, stomach pain, constipation, diarrhea, nausea, tongue and tooth disorders, dry mouth, aggravated allergy symptoms, swelling of the body including the face, fever, flu-like symptoms, thirst, cold sore, infections, muscle and/or joint pain, tremor, dizziness, migraine, depression, nightmares causing sleep disturbances, fatigue, loss of voice, bronchitis, shortness of breath, wheezing, acne, skin rashes and high blood pressure.

In addition to some of the above side effects, the following post-market side effects have been seen: nasal septum perforation.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom/effect | | Talk with your doctor or pharmacist | | Stop taking drug and seek immediate emergency medical attention |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Rare** | Immediate hypersensitivity: an allergic reaction which may cause sudden onset of wheezing or difficulty in breathing shortly after taking this medication | | | √ **(immediate help required)** |
| **Uncommon** | Chest pain, irregular or fast heartbeat | | | √ |

IF YOU EXPERIENCE ANY UNDESIRABLE OR TROUBLESOME EFFECTS, INCLUDING ANY THAT ARE NOT LISTED, ADVISE YOUR PHYSICIAN OR PHARMACIST.

## HOW TO STORE IT

KEEP OUT OF THE REACH OF CHILDREN.

- Store between 2° and 25°C (36° and 77°F).
- Protect from light.
- Do not freeze.
- Do not use this product after the expiration date on the package.

When NASONEX ALLERGY AND CONGESTION 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.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

***Drug testing for sports events:*** This product is a corticosteroid for nasal administration. Although it is not measurable in the blood, corticosteroids may be detected in the urine during drug testing. Thus, prior written permission for its use may be required by sports agencies.

You may want to read this leaflet again. Do not throw it away until you have finished your medication.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor at:

Schering-Plough Canada Inc.
Kirkland, Québec
H9H 4M7
1-866-241-3891

This leaflet was prepared by Schering-Plough Canada Inc.

Last revised: June 19, 2014

®*Registered trademark of Schering-Plough Canada Inc. Used under license.*

©*2013, 2014 Schering-Plough Canada Inc., a subsidiary of* ***Merck & Co., Inc.*** *All rights reserved.*