

## PRODUCT MONOGRAPH

Pr OMNARIS™  
(ciclesonide nasal spray)

50 mcg/metered spray

Corticosteroid for nasal use



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Date of Revision:  
April 23, 2008

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**OMNARIS™**  
(ciclesonide nasal spray)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Nasal	Spray 50 mcg/spray	<i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.</i>

**INDICATIONS AND CLINICAL USE**

OMNARIS™ (ciclesonide nasal spray) is indicated for:

- the treatment of seasonal allergic rhinitis, including hayfever, and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

**Geriatrics (> 65 years of age)**

A total of 31 patients 65 years of age and older (age range 65 to 75 years) have been treated with OMNARIS™ 200 mcg/day for up to 1 year. The adverse reactions reported in this population were similar in type and incidence to those reported by younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for OMNARIS™, no adjustment of dosage of OMNARIS™ in geriatric patients is warranted.

**Pediatrics**

OMNARIS™ is not presently approved for use in patients younger than 12 years of age. A total of 91 patients 12-17 years of age were treated with OMNARIS™ for up to one year. No differences in the rate or incidence of adverse events were observed.

**CONTRAINDICATIONS**

- OMNARIS™ is contraindicated in patients with a hypersensitivity to any of the ingredients. For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- OMNARIS™ should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract.

## WARNINGS AND PRECAUTIONS

### **Carcinogenesis and Mutagenesis**

See TOXICOLOGY.

### **Immune**

Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults on corticosteroids. In children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

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

### **Infection**

In clinical studies with corticosteroids administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* have been reported only rarely.

When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with the intranasal steroid. Therefore, patients using intranasal corticosteroids over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

OMNARIS™ should be used with caution, if at all, in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

### **Systemic Effects**

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. The risk of glaucoma was evaluated by assessments of intraocular pressure in 390 adolescent or adult patients receiving treatment with OMNARIS™ 200 mcg daily for up to 52 weeks. In this trial, no significant differences in intraocular pressure changes were observed between OMNARIS™ and placebo-treated patients. Additionally, no significant differences between OMNARIS™ 200 mcg and placebo-treated patients were noted during the 52-week study of 577 patients in which thorough ophthalmologic assessments were performed including evaluation of cataract formation using slit lamp examinations.

Although systemic effects have been minimal with recommended doses of OMNARIS™, any such effect is likely to be dose dependent. Therefore, larger than recommended doses of OMNARIS™ should be avoided. When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur. If such changes occur, the dosage of OMNARIS™ should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy.

Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. To minimize the systemic effects of intranasal corticosteroids each patient should be titrated to his/her lowest effective dose.

### **Systemic Steroid Replacement by a Topical Steroid**

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

### **Special Populations**

**Pregnant Women:** There are no adequate and well-controlled studies with OMNARIS™ in pregnant women. As with other corticosteroids, ciclesonide should only be used during pregnancy when the potential benefit to the mother justifies the potential risk to the mother, fetus or infant. Infants born to mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

The extent of exposure in pregnancy during clinical trials: Very Limited: individual cases only

**Nursing Women:** It is unknown if ciclesonide is excreted in human milk. As with other corticosteroids, OMNARIS™ should only be used in nursing women when the potential benefit to the mother justifies the potential risk to the mother and/or infant.

**Pediatrics:** OMNARIS™ is not presently approved for use in patients younger than 12 years of age. A total of 91 patients 12-17 years of age were treated with OMNARIS™ for up to one year. No differences in the rate or incidence of adverse events were observed.

**Geriatrics (> 65 years of age):** A total of 31 patients above 65 years of age (age range 65 to 75 years) have been treated with OMNARIS™ 200 mcg/day for up to 1 year. The adverse reactions reported in this population were similar in type and incidence to those reported by younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for OMNARIS™, no adjustment of dosage of OMNARIS™ in geriatric patients is

warranted.

### **Monitoring and Laboratory Tests**

As with any long-term treatment, patients using OMNARIS™ over several months or longer should be examined periodically for possible changes in the nasal mucosa.

## **ADVERSE REACTIONS**

### **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.*

In controlled clinical studies, a total of 2013 patients ages 12 years and older received treatment with OMNARIS™. In studies of 2 to 6-weeks duration, 677 patients were treated with OMNARIS™ 200 mcg daily, and in a study of up to one year in duration, 441 patients were treated with OMNARIS™ 200 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS™ was comparable to that in patients treated with the placebo. Approximately 2% of patients treated with OMNARIS™ 200 mcg in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo.

The table below displays adverse events, assessed as likely or definitely related to treatment by the investigator, that occurred with an incidence of 1% or greater in clinical trials of 2 to 6-weeks in duration.

**Table 1: Common Adverse Reactions<sup>1</sup> (1-10%) in Controlled Clinical Trials 2 to 6-weeks in Duration in Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis**

<b>Adverse Reaction</b>	<b>OMNARIS™ 200 mcg n=677 (%)</b>	<b>Placebo n= 674 (%)</b>
Epistaxis <sup>2</sup>	2.7	2.1
Nasal Passage Irritation <sup>3</sup>	2.4	2.2
Headache	1.3	0.7

<sup>1</sup>assessed as likely or definitely related to the treatment by investigator

<sup>2</sup>epistaxis (e.g. frank bleeding, blood-tinged mucus and blood flecks)

<sup>3</sup>nasal passage irritation includes nasal discomfort

In a 52-week long-term safety trial that included 663 adolescent and adult patients (227 males and 436 females) with perennial allergic rhinitis, the adverse event profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse events considered likely or definitely related to OMNARIS™ that were reported at an incidence of 1% or greater are presented in Table 2. No patient experienced a nasal septal perforation or nasal

ulcer during long-term use of OMNARIS™ nor was there any evidence of HPA-axis suppression in this study.

**Table 2: Common Adverse Reactions<sup>1</sup> (1-10%) in a 52-week Study in Adult and Adolescent Patients with Perennial Allergic Rhinitis**

Adverse Reaction	OMNARIS™ 200 mcg n=441 (%)	Placebo n= 222 (%)
Epistaxis <sup>2</sup>	8.4	6.3
Nasal passage irritation <sup>3</sup>	4.3	3.6
Headache	1.6	0.5

<sup>1</sup>assessed as likely or definitely related to the treatment by investigator

<sup>2</sup>epistaxis (e.g. frank bleeding, blood-tinged mucus and blood flecks)

<sup>3</sup>nasal passage irritation includes nasal discomfort

The following less common adverse reactions (assessed as possibly related to treatment by the investigator) were reported in controlled clinical trials 2 to 52 weeks in duration in patients 12 years of age and older with Seasonal Allergic or Perennial Allergic Rhinitis treated with OMNARIS™ 200 mcg:

### **Less Common Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)**

**Gastrointestinal:** dry mouth (0.2%), dyspepsia (0.2%)

**Infections:** candidiasis (0.2%), rhinitis (0.2%),

**Investigations:** laboratory test abnormal NOS (0.2%), white blood cell count increased (0.3%),

**Nervous System:** dysgeusia (0.2%)

**Respiratory, Thoracic and Mediastinal:** nasal dryness (0.4%), pharyngolaryngeal pain (0.4%), rhinorrhoea\* (0.3%), nasal septum disorder (0.2%), throat irritation\* (0.2%)

\*occurred at rates ≤ placebo

### **Special Populations**

The incidence of adverse events did not differ appreciably based on age, gender or race.

### **Abnormal Hematologic and Clinical Chemistry Findings**

Examination of the percentage of patients with normal values at baseline and values above or below the normal range at the end of treatment did not demonstrate any trends with respect to changes in hematology and biochemistry values, see Less Common Clinical Trial Adverse Drug Reactions above.

## **DRUG INTERACTIONS**

### **Overview**

*In vitro* data indicate that cytochrome P 450 3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide (M1) in man.

Based on *in vitro* studies in human liver microsomes, the active metabolite (M1) did not significantly inhibit or induce the metabolism of other drugs. Based on *in vitro* human hepatocyte studies, ciclesonide and M1 had no significant effect on the induction of major cytochrome P 450 isozymes. *In vitro* studies also demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating that protein binding-based drug interactions are unlikely.

The serum levels of ciclesonide and its active metabolite M1, are negligible following administration of ciclesonide nasal spray. Therefore, the potential for clinically relevant drug-drug interactions is very low. However, co-administration with potent inhibitors of the cytochrome P 450 3A4 system (e.g. protease inhibitors for the treatment of HIV infections such as, ritonavir or nelfinavir) should be considered with caution because there might be an increase in systemic drug levels of the active metabolite M1.

### **Drug-Drug Interactions**

A drug interaction study with orally inhaled ciclesonide and oral erythromycin, a substrate and weak inhibitor of cytochrome P 450 3A4, had no relevant effect on the pharmacokinetics of either M1 or erythromycin. In a drug interaction study at steady state with orally inhaled ciclesonide and oral ketoconazole, a potent cytochrome P 450 3A4 inhibitor, the exposure of the active metabolite M1 increased approximately 3.5-fold, while levels of ciclesonide remained unchanged. Due to the low systemic exposure of intranasal ciclesonide relative to orally inhaled ciclesonide, clinically relevant drug interactions with OMNARIS™, except with very potent inhibitors of the cytochrome P450 3A4 system, are not expected.

### **Drug-Food Interactions**

Interactions with food have not been established. Drug-food interactions are unlikely for intranasal corticosteroids.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established. Drug-laboratory interactions are unlikely for intranasal corticosteroids.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. Since the effect of OMNARIS™ depends on its regular use, patients should be instructed to use the nasal inhalation at regular intervals and not, as with other nasal sprays, as they feel necessary.

### **Recommended Dose and Dosage Adjustment**

**Adults and Adolescents (12 Years of Age and Older):** The recommended dose of OMNARIS™ is 200 mcg per day administered as 2 sprays (50 mcg/spray) in each nostril once daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

### **Missed Dose**

It is very important that OMNARIS™ is used regularly. If a dose is missed, the next dose should be taken when it is due and patients should not exceed the prescribed daily dosage.

### **Administration**

Prior to initial use, OMNARIS™ must be shaken gently and then the pump must be primed by actuating 8 times. If not used for 4 or more consecutive days, it should be shaken gently and reprimed with 1 spray or until a fine spray appears. It is recommended that the applicator tip be wiped with a clean tissue following daily use. It is also recommended that the applicator be cleaned weekly using warm water and reprimed with one spray or until a fine mist appears.

OMNARIS™ delivers 50 mcg of ciclesonide per spray. Each bottle of OMNARIS™ contains 120 metered sprays after initial priming. The bottle should be discarded after 120 sprays following initial priming, since the amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled dose. If more than 6 months have elapsed since the bottle was removed from the foil pouch, it should be discarded.

Do not spray in eyes.

## **OVERDOSAGE**

Acute overdosage with this dosage form is unlikely since one 120 spray bottle of OMNARIS™ only contains approximately 9.6 mg of ciclesonide. A single oral dose of up to 10 mg of ciclesonide in healthy volunteers was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Considering the low systemic availability of ciclesonide administered intranasally or orally, systemic effects following an overdose are unlikely.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Ciclesonide is a pro-drug with a low glucocorticoid receptor affinity and is pharmacologically inactive. Following intranasal application, ciclesonide is enzymatically converted by esterases in the nasal mucosa to the pharmacologically active metabolite, 21 des-methylpropionyl-ciclesonide (des-CIC, M1). M1 has potent anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound and 12 times higher than dexamethasone.

The primary mechanism of corticosteroid action in allergic rhinitis is considered due to anti-inflammation. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic inflammation. The anti-inflammatory properties of ciclesonide and M1 were shown in several *in vitro* and *in vivo* investigations, including experiments using a guinea pig model of allergic rhinitis and several investigations in primary human nasal epithelial cells, bronchial epithelial and smooth muscle cells (see DETAILED PHARMACOLOGY).

### **Pharmacodynamics**

Ciclesonide is a topical glucocorticosteroid delivered as a unique hypotonic suspension that has local anti-inflammatory properties at doses that are minimally systemically active. The effects of ciclesonide nasal spray on the HPA (hypothalamic-pituitary-adrenal) axis were investigated in several Phase III clinical trials up to one-year in duration and no appreciable effects of intranasally administered ciclesonide on serum or urinary cortisol levels were detected (see DETAILED PHARMACOLOGY). This pharmacodynamic finding is consistent with the negligible systemic bioavailability of ciclesonide following intranasal administration.

### **Pharmacokinetics**

**Absorption:** Ciclesonide and des-ciclesonide (M1) have negligible oral bioavailability (both less than 1%) due to low gastrointestinal absorption and high first-pass metabolism. The intranasal administration of ciclesonide at recommended doses results in negligible serum concentrations of ciclesonide and its active metabolite (M1) in adult and pediatric subjects using a sensitive bioanalytical assay with a lower limit of quantification of 25 pg/mL and 10 pg/mL for ciclesonide and M1, respectively. Due to the negligible serum concentrations following intranasal administration of ciclesonide, pharmacokinetic calculations could not be performed.

**Distribution:** The volumes of distribution of ciclesonide and M1 following i.v. administration were approximately 2.9 L/kg and 12.1L/kg, respectively. The percentage of ciclesonide and the active metabolite M1 bound to human plasma proteins averaged  $\geq 99\%$  each. Only the unbound drug in the systemic circulation (approximately 1%) is available for further systemic pharmacodynamic effect. M1 is not significantly bound to human transcortin.

**Metabolism:** Intranasal ciclesonide is primarily hydrolyzed to its biologically active metabolite, M1, by esterases in the nasal mucosa (primarily by carboxylesterases and cholinesterases). M1 is metabolized in the liver to inactive metabolites mainly by the CYP 3A4 isozyme. Furthermore, inactive fatty acid ester conjugates of M1 in human nasal epithelial cells were detected *in vitro* for up to 24 hours, providing a reversible depot of M1 due to gradual hydrolysis by lipases.

**Elimination:** After oral and intravenous administration, ciclesonide is predominantly excreted via the feces (66%), indicating that excretion via the bile is the major route of elimination.

### **Special Populations and Conditions**

The pharmacokinetics of intranasally administered ciclesonide have not been assessed in patient subpopulations because the resulting blood levels are insufficient for pharmacokinetic

calculations. However, the pharmacokinetic characteristics of M1 after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject/patient characteristics such as body weight, advanced age, race, gender and liver impairment. Studies in renal impaired patients were not conducted since renal excretion of M1 is a minor route of elimination ( $\leq 20\%$ ). Because the systemic exposure of intranasally administered ciclesonide is much lower than that of orally inhaled ciclesonide, it is not likely that these special populations will experience clinically relevant changes in the pharmacokinetics of intranasally administered ciclesonide.

## **STORAGE AND STABILITY**

Store at room temperature (15°C - 30°C) with the valve up. Do not freeze. Shake gently.

## **SPECIAL HANDLING INSTRUCTIONS**

The ciclesonide nasal spray device is packaged within a tamper resistant foil pouch to protect the product from oxygen absorption. In addition, a sachet containing beads of iron powder/zeolites is contained within the overwrap to absorb atmospheric oxygen. OMNARIS™ should be stored in the foil pouch and only removed immediately before first use. OMNARIS™ should be discarded 6 months after removal from pouch.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

OMNARIS™ is an unscented, metered-dose, manual-pump spray formulation containing a hypotonic aqueous suspension of ciclesonide. OMNARIS™ also contains disodium edetate, hydroxypropyl methylcellulose, microcrystalline cellulose and carboxymethylcellulose sodium, potassium sorbate and purified water; hydrochloric acid may be added to adjust the pH to a target 4.5.

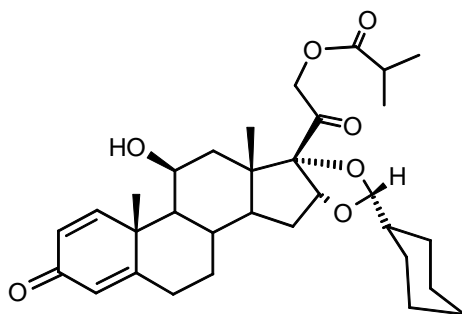
OMNARIS™ is contained within an amber glass bottle within a protective plastic sleeve and shrink wrap label and provides for nasal delivery with a manual metered pump. OMNARIS™ provides 120-metered sprays after initial priming; net fill weight 12.5 g. The OMNARIS™ bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled dose. Each spray delivers 50 mcg of ciclesonide to the patient.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:	ciclesonide
Chemical name:	[11 beta, 16 alpha (R)]-16, 17-[(Cyclohexylmethylene)-bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione
Molecular formula:	C <sub>32</sub> H <sub>44</sub> O <sub>7</sub>
Molecular mass:	540.7 g/mol
Structural formula:	



Physical Form:	White to yellow white powder
Solubility:	0.2 mg/L in water (room temperature); soluble in ethanol, acetone, methylenechloride, chloroform

## CLINICAL TRIALS

### **Study demographics and trial design**

The efficacy and safety of OMNARIS™ (ciclesonide nasal spray) in adolescents and adults 12 years and older with seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR) have been evaluated in double-blind, placebo-controlled clinical trials up to 1 year in duration. The number of patients treated with OMNARIS™ in these studies was 2013 (737 males and 1276 females) and included a total of 158 adolescent patients. The age of patients ranged from 12 – 75 years of age and the median age was 36 years. In all treatment groups, the majority of patients were Caucasian. All studies included ciclesonide 200 mcg and placebo once daily dose groups.

These trials evaluated total nasal symptoms scores that included runny nose, nasal itching, sneezing and nasal congestion using a 0 to 12 scale.

### **Study Results**

#### **Efficacy in Seasonal and Perennial Allergic Rhinitis in Adolescents and Adults:**

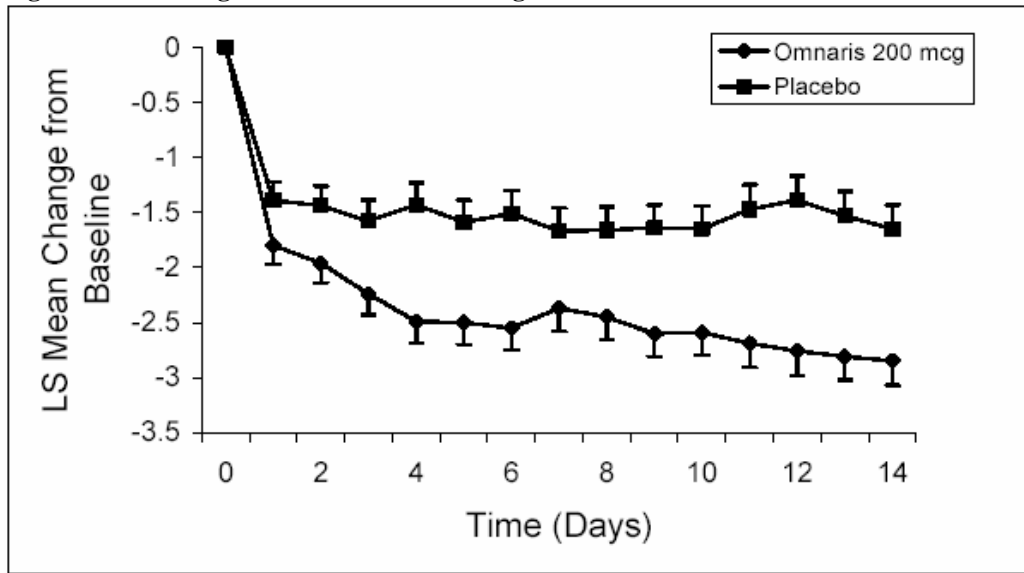
The efficacy of OMNARIS™ 200 mcg administered once daily was evaluated in two pivotal studies; a 4-week study in patients with SAR and a 6-week study in patients with PAR. The primary endpoint for these studies was change from baseline in patient-assessed total nasal symptom score (TNSS) ratings vs. placebo. The changes from baseline in TNSS over the 14 and 42 day primary efficacy assessment periods for the pivotal SAR and PAR studies in patients 12 years and older are displayed in Table 3 and Figure 1 and Figure 2 below. The mean baseline symptom scores for OMNARIS™ and placebo were 8.96 and 8.83 in SAR and 7.59 and 7.71 in PAR. In both studies, patients treated with OMNARIS™ 200 mcg once daily had a significant decrease in total nasal symptom scores compared to placebo-treated patients, and the improvement in TNSS was maintained over the full 24-hour dosing interval.

**Table 3: Mean Change from Baseline in Average Reflective AM and PM TNSS in Pivotal Efficacy Trials with OMNARIS™**

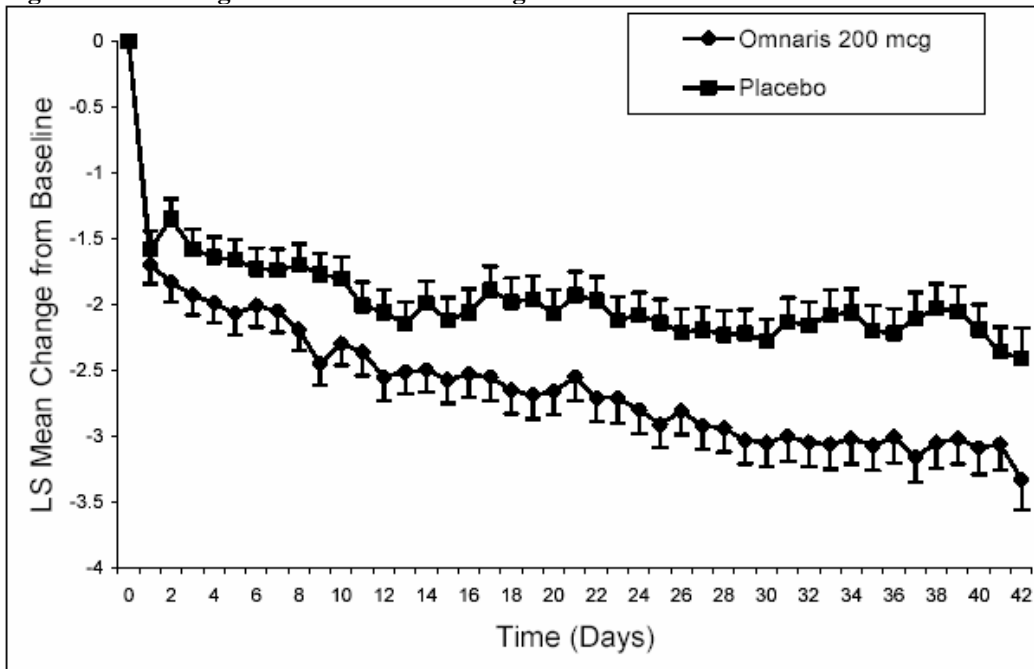
Study	Inclusion	Treatment arms / dosage (mcg)	# of patients (ITT)	Duration of Study	Total Nasal Symptom Score (TNSS)	
					LS Mean Change from baseline in Average Reflective AM and PM TNSS	p value vs. placebo
1	History of SAR for a min. of 2 years preceding study season.	CIC 200 OD	162	4 weeks <sup>1</sup>	-2.40	p<0.001
		PLACEBO	162		-1.50	
2	History of PAR for a min. of 2 years preceding study start.	CIC 200 OD	232	6 weeks	-2.51	p<0.001
		PLACEBO	229		-1.89	

<sup>1</sup>primary efficacy endpoint was change from baseline over the first two weeks of the treatment period.  
CIC = ciclesonide

**Figure 1: Change from Baseline in Average AM and PM Reflective TNSS in Seasonal Allergic Rhinitis**



**Figure 2: Change from Baseline in Average AM and PM Reflective TNSS in Perennial Allergic Rhinitis**



The long-term effectiveness of OMNARIS™ was demonstrated in a 52-week safety study. Over the full course of the study (Days 2-365), the mean decrease in TNSS (24-hour reflective) from baseline was greater in the OMNARIS™ group vs. placebo ( $p < 0.001$ ) with no evidence of tachyphylaxis.

In addition to the two pivotal efficacy studies, two Environmental Exposure Unit (EEU) studies were conducted in patients with SAR to investigate the onset of effect of OMNARIS™. In the first EEU study a statistically significant improvement in nasal symptoms compared to placebo was noted within 1 hour of first using ciclesonide nasal spray. In a second EEU study in seasonal allergic rhinitis patients, statistically significant improvement in nasal symptoms was observed at one time point of 6 hours, however, a second statistically significant confirmatory time point was not observed.

## DETAILED PHARMACOLOGY

### Human Pharmacology

**Pharmacokinetics:** Ciclesonide, administered as a nasal spray, at recommended doses results in negligible serum concentrations of ciclesonide and its active metabolite (M1), despite the use of a sensitive assay with a lower quantitation limit of 25 pg/mL for ciclesonide and 10 pg/mL for the M1. Thus, no pharmacokinetic data for this dosage form could be calculated.

Investigations in primary human nasal epithelial cells (HNEC), bronchial epithelial and smooth muscle cells have shown rapid cell penetration of ciclesonide, conversion to active metabolite M1, and a long duration of anti-inflammatory action *in vitro*.

In studies in HNEC it was demonstrated that the pharmacological active metabolite M1 can reversibly form fatty acid conjugates (primary oleate) which can serve as a slow release pool for the active metabolite in nasal tissue. The long-term retention of M1 at relatively stable levels for up to 24 hours was demonstrated. These properties contribute to long-term retention of M1 in the cells.

**Pharmacodynamics:** The effects of OMNARIS™ on adrenal function have been evaluated in several clinical trials. In a study of 40 healthy adult volunteers and 8 asymptomatic seasonal allergic rhinitis patients, no significant differences between the active and placebo groups were observed in 24-hour plasma or urine cortisol after administration of 50-800 mcg daily of ciclesonide for 14 days. In a 1 year safety study including 174 patients treated with 200 mcg once daily of OMNARIS™ and 92 patients treated with placebo who had cortisol assessments, no significant differences in morning plasma and 24-hour urine cortisol levels were observed with ciclesonide versus placebo treatment.

As asthma and allergic rhinitis are often co-morbid conditions, the concomitant use of intranasal and inhaled corticosteroids was studied. Two pharmacodynamic studies were conducted in patients with perennial allergic rhinitis to assess the effect of OMNARIS™ on adrenal function when combined with inhaled corticosteroid-containing products. One study evaluated the addition of OMNARIS™ to inhaled beclomethasone dipropionate HFA (320 mcg BID) in 111 patients. A second study evaluated the addition of OMNARIS™ to inhaled fluticasone propionate and salmeterol (500/50 mcg BID) combination therapy in 150 patients. Orally inhaled corticosteroid treatment was administered for a ten-day run-in period and was continued throughout a 43-day treatment period. Patients were randomized to concomitant ciclesonide (200

mcg/day) or placebo nasal spray at the end of the run-in period. As a positive control on the last treatment day, all patients additionally received 2 mg dexamethasone orally.

Both 24-hour plasma and urine cortisol levels significantly decreased over the 10-day run-in period due to the inhaled corticosteroid therapy. After six weeks of treatment, OMNARIS™, when co-administered with inhaled corticosteroid therapy, was shown to have no additional inhibitory effect on plasma or urine cortisol when compared to placebo. In both studies, further cortisol suppression was observed on the last treatment day when oral dexamethasone was added, indicating that additional suppression of the HPA-axis was possible. These studies indicate that the addition of OMNARIS™ is unlikely to impact the HPA-axis in patients concurrently receiving inhaled corticosteroids.

### **Animal Pharmacology**

The main mechanism of corticosteroid action in allergic rhinitis is considered due to anti-inflammation. The anti-inflammatory properties of ciclesonide and des-CIC (M1) were shown in several *in vitro* and *in vivo* experiments. In a guinea pig model of allergic rhinitis, it was demonstrated that the repeated treatment with ciclesonide could prevent the immediate (increase in nasal resistance) and late response (influx of inflammatory cells) following allergen challenge.

OMNARIS™ is formulated as a hypotonic suspension. In a preclinical study conducted in rabbits, there was an enhanced uptake of ciclesonide into the nasal mucosa, a significantly higher intracellular concentration of M1 and longer retention of the active metabolite when a hypotonic suspension of ciclesonide was administered compared to administration of an isotonic formulation.

## TOXICOLOGY

Toxicology studies conducted with ciclesonide showed effects typically associated with administering high doses of glucocorticoids; no unexpected effects were found in the toxicology studies conducted with ciclesonide.

### Acute toxicity

Oral and intraperitoneal acute toxicity studies were performed in rats and mice.

The approximate LD<sub>50</sub> values are significantly higher than doses that would be administered to humans:

**Table 4: LD<sub>50</sub> Values in Oral and Intraperitoneal Acute Toxicity Studies**

Species	Route	Doses (mg/kg)	LD <sub>50</sub> (mg/kg)
Mouse	Intraperitoneal	0, 50, 100, 200	>200
Mouse	Oral	0, 2000	>2000
Rat	Intraperitoneal	0, 50, 100, 200	>200
Rat	Oral	0, 2000	>2000

### Chronic Toxicity

In all toxicity studies, ciclesonide was well tolerated by animals of all investigated species with adverse effects limited to those associated with glucocorticoid activity that were either completely or mostly reversible after cessation of treatment. There was no indication of clinically relevant effects in the respiratory tract.

**Table 5: No Observed Adverse Effect Level in Chronic Toxicity Studies with Intranasal Application of Ciclesonide**

Species	Duration	Application form	NOAEL (µg/kg/day)
Rat	4 weeks	Intranasal (hypotonic suspension)	429
Rat	4 weeks	Intranasal (hypotonic suspension)	429
Dog	4 weeks	Intranasal (hypotonic suspension)	480
Dog	6 months	Intranasal (hypotonic suspension)	4800 µg/body/day

In both rat studies, a reduction in weight gain, slight deviations in clinical chemistry parameters, and a reduction in thymus weight reflected the pharmacological activity of ciclesonide. All findings were reversible.

The 4-week study in dogs revealed a reduction in body weight gain, elevation of clinical chemistry parameters, and low thymus and adrenal weights correlating with thymus and adrenal atrophy. The lymphoid aggregates associated with the respiratory mucosa tended to be smaller. All findings were attributed to the glucocorticoid pharmacology of ciclesonide and showed reversibility after the treatment-free period.

In the 6-month dog study, substance-related findings included a slight decrease in leukocyte and lymphocyte count, low adrenal weights, cortical and thymus atrophy and atrophy of the mucosal-associated lymphoid tissue in the respiratory mucosa of the nasal cavity. All these findings were very slight or slight, showed complete reversibility after the recovery period and are considered to be due to the glucocorticoid pharmacological action of ciclesonide.

Inhalation administration of ciclesonide was evaluated in a series of studies of up to 6-months duration in rats and 12-months duration in dogs, and the no observed adverse effect levels (NOAEL) were determined.

**Table 6: No Observed Adverse Effect Level in Chronic Toxicity Studies with Inhalation Administration of Ciclesonide**

Species	Duration	Application form	NOAEL (µg/kg/day)
Rat	4 week	Powder	50.5
Rat	4 week	MDI	Males: 50.3; Females 55.2
Rat	6 months	Powder	Males: 44.5; Females 49.6
Dog	4 week	Powder	50
Dog	4 week	MDI	61
Dog	4 week	MDI	15 (highest dose studied)
Dog	13 week	MDI	53
Dog	12 month	Powder	47

In the rat, comparable and typical glucocorticoid-like effects were observed which were completely or partially reversible during the recovery periods – slight reductions in body, spleen and thymus weights and minor alterations in erythrocytes, lymphocytes, differential blood cell picture, serum urea, serum creatinine, serum corticosterone and urine electrolyte levels, increased development of alveolar structures in the mammary gland, atrophy of lymphocytic components in thymus, spleen, and lymph nodes, atrophy of adrenal cortex.

Dogs similarly showed only exaggerated glucocorticoid-like effects – atrophy of lymphocytic components in thymus, spleen and lymph nodes, suppression of serum cortisol levels, atrophy of adrenal cortex.

The initial effects seen in toxicity studies – decrease of body-weight gain, lymphoid tissue depletion, adrenal atrophy, and, in rats, activation of erythrocyte parameters - result from pronounced pharmacological glucocorticoid activity, demonstrating the continuum of actions recognized for corticosteroids and seen with other glucocorticoids. Because of the need for the enzymatic conversion of ciclesonide ester to its active metabolite and the high plasma protein binding of both ciclesonide and its metabolite, the results suggest that ciclesonide can be used in

humans at therapeutic doses that are expected to be devoid of both local (upper and lower respiratory tract, mouth, esophagus, stomach) and systemic glucocorticoid effects.

### **Local Tolerance**

In a primary eye irritation study, ciclesonide nasal spray with the concentrations 25 and 100 mcg/actuation was categorized as non-irritant. The formulation of the nasal spray showed no primary irritating potential in an intranasal irritation study in rabbits.

### **Mutagenicity**

Ciclesonide was negative in the conducted *in vitro* test for genotoxicity:

- in the Ames test for gene mutation in bacteria;
- in the HPRT test for gene mutation in bacteria;
- in the test for chromosome aberrations in human lymphocytes and the *in vitro* micronucleus test in Chinese hamster V79 cells.

Moreover, racemic ciclesonide was also negative in an Ames test.

Four independent *in vivo* micronucleus tests were performed in mice covering a range of orally administered doses of glucocorticoids including ciclesonide. Threshold doses were found for all glucocorticoids tests at a dose which induced micronuclei *in vivo*. This induction of micronuclei is known from the literature. A positive response at high doses of glucocorticoids in the *in vivo* micronucleus assays is not indicative for a genotoxic potential.

### **Carcinogenicity**

Two carcinogenicity studies were performed with ciclesonide; one study was conducted in mice (2-year study, oral gavage) and the other in rats (2-year study, inhalation).

Doses in the mouse study were 150, 450, and 900 mcg/kg/day administered by oral gavage. No compound related malignant tumors were reported. However, histology showed small, focal and solitary gastric adenomas at a very low incidence (one male and three females in the high dose group, one male each in the low and mid dose group). The adenoma were small, focal, solitary, and incidentally observed at the end of the 2-year study. They did not affect survival rate and only reached statistical significance by trend analysis in high dose females. There were also non-neoplastic changes consisting of a slightly increased incidence of hyperplastic changes in the epithelium of the antrum, mainly at the junction with the duodenum (mainly in males), and focal squamous metaplasia at the junction of the antrum and duodenum were detected for mice receiving 900 or 450 mcg/kg/day. The benign gastric adenomas in mice were only present in one species (mouse), only in one site (the antrum of the stomach), and only by one route of administration (oral gavage). For the oral gavage in the mouse, polyethylene glycol 400 (PEG 400) was used as the vehicle. PEG 400 has been reported to be a digestive tract irritant and to potentiate the activity of drugs. There is no PEG in the clinical nasal spray formulation. Hyperplastic and neoplastic changes in the stomach of the mice should be seen together as the result of response processes to irritating action. The benign neoplastic findings in the antrum are unlikely to present a safety concern for humans.

Inhalation doses in the rat carcinogenicity study were for males/females, 14/16.2, 34.9/40.4, and 89.3/103.6 mcg/kg/day administered by MDI over one hour. After 2 years of daily exposure, the results of the rat inhalation carcinogenicity study indicate the absence of a tumorigenic potential of inhaled ciclesonide.

### **Reproduction and Teratology**

No effects were observed in rats on fertility, embryofoetal development, or pre/post natal studies apart from a reduction in body weight or body weight gain in animals receiving 300 mcg/kg/day and 900 mcg/kg/day orally (all studies were conducted with 100/300/900 mcg/kg/day). In rabbits, embryotoxic effects (reduced litter weight, incomplete ossification) and teratogenic effects (like cleft palate, flexure of paw, enlarged fontanelle, parchment-like skin) were observed over the dose range of 5 to 100 mcg/kg/day given subcutaneously. The effects observed with ciclesonide in rabbits are those reported for other glucocorticosteroids. The no-effect for maternal toxicity in rabbits was established at 25 mcg/kg/day and for embryofoetal development at 1 mcg/kg/day.

## REFERENCES

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## PART III: CONSUMER INFORMATION

**OMNARIS™**  
(ciclesonide nasal spray)

**IMPORTANT: PLEASE READ**

This leaflet is part III of a three-part "Product Monograph" published when OMNARIS™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OMNARIS™. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

OMNARIS™ is a corticosteroid for use in adults and adolescents 12 years of age or older, to relieve the symptoms that may occur with hay fever [seasonal allergic rhinitis (SAR)] or other year-round allergies [perennial allergic rhinitis (PAR)], including stuffiness/congestion in the nose, runny nose, itching and sneezing.

**What it does:**

OMNARIS™ is a medication that is used in the nose. When taken according to the directions, OMNARIS™ can help relieve nasal congestion (blocked nose), runny nose, itching and sneezing. It reduces inflammation in the lining of the nose and nasal passages.

The therapeutic effects of corticosteroids like OMNARIS™ are not immediate. It may take a few days for this medicine to work. It is very important that you use it regularly. Do not stop treatment even if you feel better unless told to do so by your doctor.

**When it should not be used:**

Do not use this medication if:

- you are allergic to any of the ingredients in OMNARIS™;
- you have an untreated infection of the nose (i.e. yellow or green discharge from the nose);
- your nose was recently operated on or injured. You may be told to wait until healing has occurred before using OMNARIS™.

**What the medicinal ingredient is:**

Ciclesonide

**What the important nonmedicinal ingredients are:**

OMNARIS™ contains disodium edetate, hydrochloric acid, hydroxypropylmethylcellulose, microcrystalline cellulose and carboxymethylcellulose sodium, potassium sorbate and purified water.

**What dosage forms it comes in:**

OMNARIS™ comes in a bottle with a manual metered pump. Each spray activation delivers 50 micrograms of OMNARIS™ in a metered dose.

**WARNINGS AND PRECAUTIONS****BEFORE you use OMNARIS™ talk to your doctor or pharmacist:**

- About all health problems you have now or have had in the past;
- About all the medicines you take, including those you can buy without a prescription;
- If you ever had to stop taking other medicines for hay fever or other allergies because you were allergic to them or experienced other problems;
- If you have a history of tuberculosis (TB) infections;
- If you have sores in the nose;
- If you have an infection (fungal, bacterial, or viral)
- If you have herpes simplex (virus) infection of the eye;
- If you are taking other steroid medicine by mouth or by inhalation (breathing in);
- If you are taking drugs that suppress the immune system;
- If you are pregnant, plan to become pregnant or are breastfeeding. Do not use this medication during pregnancy or breastfeeding without first discussing it with your doctor.

**INTERACTIONS WITH THIS MEDICATION**

Talk to your doctor or pharmacist if you are taking ketoconazole, itraconazole, ritonavir, or nelfinavir. These drugs may interact with OMNARIS™.

**PROPER USE OF THIS MEDICATION**

Your doctor will decide what an appropriate dosage of OMNARIS™ is for you.

Your doctor or pharmacist has explained when and how to take OMNARIS™. Follow your doctor or pharmacist's directions carefully – they may be different from the information provided in this leaflet.

OMNARIS™ should be taken once daily.

**Usual dose:**

**Adults and Adolescents (12 Years and Older):** The recommended dosage is 2 sprays in each nostril once daily (total daily dose, 200 micrograms).

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 micrograms/day).

OMNARIS™ is not presently approved for use in patients younger than 12 years of age.

**How to Use OMNARIS™ Properly:**

**Preparing For Use:**

1. Remove OMNARIS™ from its tamper proof foil pouch and write the date of opening on the sticker provided. Peel off this sticker and place it on your nasal spray bottle. It's important to throw away the nasal spray bottle 6 months after this date.
2. Shake the bottle gently and prime the pump by pressing downward on the shoulders of the applicator eight times. Read the complete instructions carefully and use only as directed. If unused within 4 or more consecutive days, reprime by spraying one time or until a fine mist appears. There is enough medication in this bottle to allow for the required priming and repriming, in addition to the 120 doses.

**Using the Spray:**

1. Blow your nose to clear your nostrils if needed.
2. Shake the bottle gently and remove the cap.
3. Hold the bottle firmly with your index and middle finger on either side of the spray tip while supporting the base of the bottle with your thumb (Figure 1).



4. Insert spray tip into one nostril, and close the other nostril with your finger (Figure 2).



5. Tilt your head forward slightly and keeping the bottle upright, press the pump quickly and firmly and inhale through your nose as you spray (Figure 3).  
**Avoid spraying in eyes or directly onto the nasal septum.**



6. If a second spray is required in this nostril, repeat steps 3-5. Repeat steps 3-6 for the other nostril.

**Applicator Cleaning Instructions:**

After daily use of your nasal spray, wipe the applicator tip with a clean tissue and replace the cap.

On a weekly basis or if the nasal applicator is clogged at any time, use the following cleaning instructions (**Do not try to unblock the tiny spray hole on the nasal applicator with a pin or other sharp object**):

1. Remove the cap and then gently pull upwards to free the nasal applicator.
2. Wash the cap and applicator with warm water.
3. Dry and replace the nasal applicator.
4. Prime the unit with one spray or until a fine mist appears.
5. Replace the cap.

**How To Know When Your Nasal Spray Bottle Is Empty:**

The amount of nasal spray left can be seen through a window on the bottle. You should discard the bottle after using 120 sprays or 6 months after opening the foil pouch, whichever comes first.

**Overdose:**

If you accidentally take more than the maximum recommended daily dose, contact your doctor or health care professional immediately.

**Missed Dose:**

It is very important that OMNARIS™ is used regularly. If a dose is missed, the next dose should be taken when it is due. Do not double dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like any medication, OMNARIS™ may cause side effects in some people. Side effects that may occur with the use of corticosteroid nasal sprays, including OMNARIS™, are headache, nose-bleeds, and burning or irritation inside the nose.

If any of these become troublesome, consult your doctor. If you experience any unusual or unexpected symptoms while using OMNARIS™, consult your doctor.

*This is not a complete list of side effects. For any unexpected effects while taking OMNARIS™, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store at controlled room temperature (15°C - 30°C). Do not freeze. Store sitting-up.

**REPORTING SUSPECTED SIDE EFFECTS**

**If you experience an adverse effect with the use of OMNARIS™, please contact your physician.**

**Adverse events may be reported to Nycomed Medical Information & Pharmacovigilance at:**

**1-866-295-4636**

**To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:**

**By toll-free telephone: 866-234-2345**

**By toll-free fax: 866-678-6789**

**Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)**

**By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)**

**By regular mail:**

**Canada Vigilance National Office  
Marketed Health Products Safety and  
Effectiveness Information Division  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9**

**NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.**

**MORE INFORMATION**

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

<http://www.nycomed.ca>

or by contacting the sponsor, Nycomed Canada Inc. at:  
1-866-295-4636

This leaflet was prepared by Nycomed Canada Inc.

Last revised: December 10, 2007