HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMNARIS® Nasal Spray safely and effectively. See full prescribing information for OMNARIS Nasal Spray.

OMNARIS® (ciclesonide) Nasal Spray
For Nasal Inhalation Only
Initial U.S. Approval: 2006

----------INDICATIONS AND USAGE----------

OMNARIS Nasal Spray is a corticosteroid indicated for treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older and perennial allergic rhinitis in adults and adolescents 12 years of age and older. (1.1, 1.2)

----------DOSAGE AND ADMINISTRATION----------

For Intranasal Use Only

- 2 sprays per nostril once daily. (200 mcg) (2.1, 2.2)
- Priming Information: Gently shake and prime OMNARIS Nasal Spray before using for the first time or when not used for four consecutive days. (2)

----------DOSAGE FORMS AND STRENGTHS----------

- Nasal Spray: 50 mcg of ciclesonide in each 70-microliter spray. (3)
- Supplied in a 12.5 g bottle containing 120 sprays. (16)

----------CONTRAINDICATIONS----------

- Patients with a known hypersensitivity to ciclesonide or any of the ingredients of OMNARIS Nasal Spray. (4)

----------WARNINGS AND PRECAUTIONS----------

- Epistaxis, *Candida albicans* infection, nasal septal perforation, impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid spraying OMNARIS Nasal Spray directly onto the nasal septum. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma. (5.1)
- Development of glaucoma or cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. (5.2)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.3)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue OMNARIS Nasal Spray slowly. (5.4)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving OMNARIS Nasal Spray. (5.5, 8.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (>2% incidence) included headache, epistaxis, nasopharyngitis, ear pain, and pharyngolaryngeal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch* for voluntary reporting of adverse events.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use only if benefit justifies potential risk to fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Seasonal Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

1.2 Treatment of Perennial Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Administer OMNARIS Nasal Spray by the intranasal route only. Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. If the product is not used for four consecutive days, it should be gently shaken and reprimed with one spray or until a fine mist appears. Illustrated patient's instructions for proper use accompany each package of OMNARIS Nasal Spray.

2.1 Seasonal Allergic Rhinitis

Adults and Children (6 Years of Age and Older): The recommended dose of OMNARIS Nasal Spray is 2 sprays per nostril once daily (200 mcg). The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

2.2 Perennial Allergic Rhinitis

Adults and Adolescents (12 Years of Age and Older): The recommended dose of OMNARIS Nasal Spray is 2 sprays per nostril once daily (200 mcg). The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).

3 DOSAGE FORMS AND STRENGTHS

OMNARIS Nasal Spray is a metered-dose, manual-pump spray formulation containing a hypotonic aqueous suspension of ciclesonide. Once primed, each actuation of the pump delivers 50 mcg ciclesonide in a volume of 70 microliters from the nasal actuator.

4 CONTRAINDICATIONS

OMNARIS Nasal Spray is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of OMNARIS Nasal Spray [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis: In clinical studies of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with OMNARIS Nasal Spray than those who received placebo [see *Adverse Reactions (6)*].

Candida Infection: In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Nasal Septal Perforation: Instances of nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. No cases of nasal septal perforation were identified in clinical studies with OMNARIS Nasal Spray. Avoid spraying OMNARIS Nasal Spray directly onto the nasal septum.

Impaired Wound Healing: 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.

5.2 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

The risk of glaucoma was evaluated by assessments of intraocular pressure in 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray 200 mcg daily for up to 12 weeks. In these studies, no significant differences in intraocular pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-treated patients. Additionally, no significant differences between OMNARIS Nasal Spray 200 mcg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed, including evaluation of cataract formation using slit lamp examinations.

5.3 Immunosuppression

Patients who are using 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 susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect 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 a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

5.4 Hypothalamic-Pituitary-Adrenal Axis Effect

Hypercorticism and Adrenal Suppression: When intranasal corticosteroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of OMNARIS Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

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.

5.5 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely (e.g., via stadiometry) in pediatric patients receiving OMNARIS Nasal Spray.

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Epistaxis, nasal septal perforations, *Candida albicans* infection, impaired wound healing [see *Warnings and Precautions (5.1)*]
- Cataracts and glaucoma [see *Warnings and Precautions (5.2)*]
- Immunosuppression [see *Warnings and Precautions (5.3)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [see *Warnings and Precautions (5.4, 5.5), Use in Specific Populations (8.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below for adults and adolescents 12 years of age and older are based on 3 clinical trials of 2 to 6 weeks duration and one 52-week trial. In the 3 trials of 2 to 6 weeks duration, 1524 patients (495 males and 1029 females, ages 12 to 86 years old) with seasonal or perennial allergic rhinitis were treated with OMNARIS Nasal Spray 200, 100, 50, or 25 mcg or placebo once daily. The racial distribution in these three trials included 1374 Caucasians, 69 Blacks, 31 Asians, and 50 patients classified as Other. The 52-week trial was conducted in 663 patients (227 males and 436 females, ages 12 to 73 years old) treated with OMNARIS Nasal Spray 200 mcg or placebo once daily. The racial distribution in this trial included 538 Caucasians, 69 Blacks, 16 Asians, and 40 patients classified as Other. The data from pediatric patients are based upon 4 clinical trials in which 1541 children (871 males and 670 females, ages 2 to 11 years old) with seasonal or perennial allergic rhinitis were treated with OMNARIS Nasal Spray 200, 100, or 25 mcg or placebo once daily for 2 to 12 weeks. The racial distribution in these four trials included 1136 Caucasians, 273 Blacks, 20 Asians, and 112 patients classified as Other.

Adults and Adolescents 12 Years of Age and Older in Short-Term (2-6 weeks) Trials: In three short-term trials conducted in the US and Canada, 546 patients were treated with OMNARIS Nasal Spray 200 mcg daily. Adverse reactions did not differ appreciably based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal Spray 200 mcg in clinical trials discontinued because of adverse reactions; this rate was similar for patients treated with placebo. The table below displays reactions that occurred with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo in clinical trials of 2 to 6 weeks in duration.

Table 1 Adverse Events from Controlled Clinical Trials 2 to 6 Weeks in Duration in Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

Adverse Event	OMNARIS Nasal Spray 200 mcg Once Daily (N = 546) %	Placebo (N = 544) %
Headache	6.0	4.6
Epistaxis	4.9	2.9
Nasopharyngitis	3.7	3.3
Ear Pain	2.2	0.6

Pediatric Patients Aged 6 to 11 Years in Short-Term (2-12 weeks) Trials: In two short-term trials, conducted in the US and Canada, 913 patients were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. Adverse events did not differ appreciably based on age, gender, or race. In clinical trials, 1.6% and 2.7% of patients treated with OMNARIS Nasal Spray 200 mcg or 100 mcg, respectively, discontinued because of adverse reactions; these rates were lower than the rate in patients treated with placebo (2.8%). Table 2 displays adverse events that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo.

Table 2 Adverse Events from Controlled Clinical Trials 2 to 12 Weeks in Duration in Patients 6 to 11 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

Adverse Event	OMNARIS Nasal Spray 200 mcg Once Daily (N = 380) %	Placebo (N = 369) %
Headache	6.6	5.7
Nasopharyngitis	6.6	5.4
Pharyngolaryngeal pain	3.4	3.3

Pediatric Patients Aged 2 to 5 Years in Short-Term (6-12 weeks) Trials: In two short-term trials conducted in the US, 183 patients were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. The distribution of adverse events was similar to that seen in the 6 to 11 year old children.

Long-Term (52-Week) Safety Trial: In a 52-week double-blind, placebo-controlled safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females) with perennial allergic rhinitis, the adverse reaction profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse reactions, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo were epistaxis, pharyngolaryngeal pain, sinusitis, headache, nasal discomfort, cough, bronchitis, influenza, back pain, and urinary tract infection. No patient experienced a nasal septal perforation or nasal ulcer during this long-term trial of OMNARIS Nasal Spray.

6.2 Post-Marketing Experience

The following adverse reactions have been reported in association with post-marketing use of the product and are not listed above: nasal congestion, nasal ulcer and dizziness. Because these reactions are reported voluntarily from a population of uncertain size and are generally not confirmed with a health care professional, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

In vitro studies and clinical pharmacology studies suggested that des-ciclesonide has no potential for metabolic drug interactions or protein binding-based drug interactions [see *Clinical Pharmacology (12.3)*].

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin following oral inhalation of ciclesonide [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. OMNARIS Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Oral administration of ciclesonide in rats at approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2 produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at less than the maximum human daily intranasal dose in adults based on mcg/m^2 produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects [see *Animal Toxicology and Pharmacology (13.2)*].

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.3 Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when OMNARIS Nasal Spray is administered to nursing women.

8.4 Pediatric Use

The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The efficacy of OMNARIS Nasal Spray in patients 6 to 11 years of age for treatment of the symptoms of seasonal allergic rhinitis was demonstrated in one study in patients 6 to 11 years of age with seasonal allergic rhinitis. The efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of seasonal allergic rhinitis in patients 5 years of age and younger has not been established. The efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of perennial allergic rhinitis in patients 11 years of age and younger has not been established [see *Clinical Studies (14.1)*]. The safety of OMNARIS Nasal Spray in children 2 to 11 years of age was evaluated in 4 controlled clinical studies of 2 to 12 weeks duration [see *Clinical Pharmacology (12.2)*, *Clinical Studies (14.1)*, and *Adverse Reactions (6.1)*].

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely (e.g., via stadiometry). A 52-week, multicenter, double-blind, randomized, placebo-controlled parallel-group study was conducted to assess the effect of orally inhaled ciclesonide on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this study because compliance could not be assured. Ciclesonide blood levels were also not measured during the one-year treatment period. There was no difference in efficacy measures between the placebo and the orally inhaled ciclesonide groups.

The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

8.5 Geriatric Use

Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

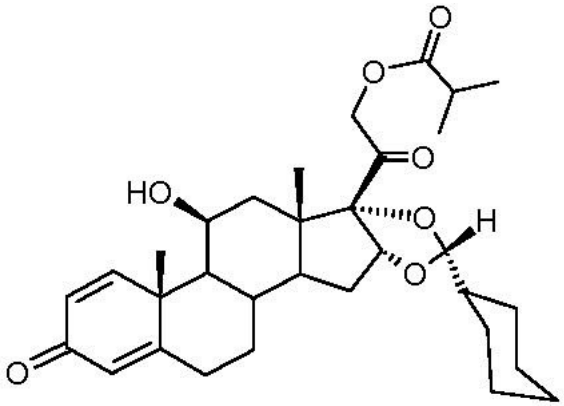
10 OVERDOSAGE

Chronic overdosage may result in signs or symptoms of hypercorticism [see *Warnings and Precautions (5.4)*].

There are no data available on the effects of acute or chronic overdosage with OMNARIS Nasal Spray.

11 DESCRIPTION

The active component of OMNARIS Nasal Spray is ciclesonide, a non-halogenated glucocorticoid having the chemical name pregna -1,4-diene-3,20-dione, 16,17-[[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α)-. Ciclesonide is delivered as the R-epimer. The empirical formula is $C_{32}H_{44}O_7$ and its molecular weight is 540.7. Its structural formula is as follows:



Ciclesonide is a white to yellow-white powder, practically insoluble in water and freely soluble in ethanol and acetone. OMNARIS Nasal Spray is a metered-dose, manual-pump spray formulation containing a hypotonic aqueous suspension of ciclesonide. OMNARIS Nasal Spray also contains microcrystalline cellulose, carboxymethylcellulose sodium, hypromellose, potassium sorbate and edetate sodium; and hydrochloric acid to adjust the pH to 4.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or RM1) following intranasal application. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound.

The precise mechanism through which ciclesonide affects allergic rhinitis symptoms is not known. 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.

12.2 Pharmacodynamics

Adrenal Function: In a 12-week study in children 6 to 11 years of age with perennial allergic rhinitis, daily doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray were compared to placebo nasal spray. Adrenal function was assessed by measurement of 24-hour urinary-free cortisol (in 32 to 44 patients per group) and morning plasma cortisol levels (in 45 to 61 patients per group) before and after 12 consecutive weeks of treatment. The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary-free cortisol compared to the placebo-treated group. The differences (and 95% confidence intervals) from placebo in the mean change from baseline to 12 weeks were -0.81 (-4.0, 2.4), -0.08 (-3.1, 2.9), and -2.11 (-5.3, 1.1) mcg/day for 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. The mean AM plasma cortisol value did not show any consistent treatment effect with differences (and 95% confidence intervals) from placebo in the mean change from baseline to 12 weeks of 0.35 (-1.4, 2.1), 0.12 (-1.5, 1.7), and -0.38 (-2.1, 1.3)

mcg/dL for 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. In this study, serum was assayed for ciclesonide and des-ciclesonide [see *Clinical Pharmacology (12.3)*].

In a 6-week study in children 2 to 5 years of age with perennial allergic rhinitis, daily doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray were compared to placebo nasal spray. Adrenal function was assessed by measurement of 24-hour urinary-free cortisol (in 15 to 22 patients per group) and morning plasma cortisol levels (in 28 to 30 patients per group) before and after 6 consecutive weeks of treatment. The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary-free cortisol compared to the placebo-treated group. The differences (and 95% confidence intervals) from placebo in the mean change from baseline to 6 weeks were -2.04 (-4.4, 0.3), -1.96 (-4.5, 0.6), and -1.76 (-4.3, 0.8) mcg/day for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. The plasma cortisol also decreased numerically after treatment with ciclesonide. The differences (and 95% confidence intervals) from placebo in the mean change in plasma cortisol from baseline to 6 weeks were -1.04 (-2.7, 0.7), -0.36 (-2.1, 1.4), and -0.12 (-1.8, 1.6) mcg/dL for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. In this study, serum was assayed for ciclesonide and des-ciclesonide [see *Clinical Pharmacology (12.3)*].

There are no adequately conducted studies in adults and adolescents that assess the effect of OMNARIS Nasal Spray on adrenal function.

12.3 Pharmacokinetics

Absorption: Ciclesonide and des-ciclesonide 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. However, the known active metabolite (des-ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide. The bioanalytical assay used has a lower limit of quantification of 25 pg/mL and 10 pg/mL, for ciclesonide and des-ciclesonide, respectively.

In healthy adults treated for two weeks with 50 to 800 mcg of ciclesonide nasal spray daily (n=6 in each treatment group), the peak serum concentrations of des-ciclesonide in all subjects were found to be below 30 pg/mL. Of those treated with 800 mcg and 400 mcg daily, 100% and 67% had detectable levels of des-ciclesonide, respectively. With daily doses of 200 mcg or less, detectable serum levels of des-ciclesonide were not observed. The low systemic exposure following ciclesonide nasal spray administration was confirmed in a crossover study in twenty-nine healthy adults. The median C_{max} was less than 10 pg/mL and 602 pg/mL following a single dose of ciclesonide nasal spray (300 mcg) and orally inhaled ciclesonide (320 mcg), respectively.

Distribution: Following intravenous administration of 800 mcg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged ≥ 99% each, with ≤ 1% of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

Metabolism: Ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by esterases. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP 2D6. The full range of potentially active metabolites of ciclesonide has not been characterized. After intravenous administration of ^{14}C-ciclesonide, 19.3% of the

resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, as yet, unidentified multiple metabolites.

Elimination: Following intravenous administration of 800 mcg of ciclesonide, the clearance values of ciclesonide and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively). ^{14}C-labeled ciclesonide was predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination. Approximately 20% or less of drug-related radioactivity was excreted in the urine.

Special Populations: The pharmacokinetics of intranasally administered ciclesonide have not been assessed in patient subpopulations because the resulting blood levels of ciclesonide and des-ciclesonide are insufficient for pharmacokinetic calculations. However, population pharmacokinetic analysis showed that characteristics of des-ciclesonide after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject characteristics such as body weight, age, race, and gender.

Hepatic Impairment: Compared to healthy subjects, the systemic exposure (Cmax and AUC) in patients with liver impairment increased in the range of 1.4 to 2.7-fold after ex-actuator administration of 1280 mcg ciclesonide via oral inhalation. Dose adjustment in liver impairment is not necessary.

Renal Impairment: Studies in renally-impaired patients were not conducted since renal excretion of des-ciclesonide is a minor route of elimination (≤ 20%).

Pediatric: In pediatric subjects treated with 25 to 200 mcg of ciclesonide nasal spray daily, serum concentrations of des-ciclesonide were below 45 pg/mL, with the exception of one value of 64.5 pg/mL. In a 12-week study in children 6 to 11 years of age with perennial allergic rhinitis, des-ciclesonide was detected in 50% of the subjects treated with 200 mcg and in 5% of those treated with 100 mcg ciclesonide nasal spray daily. In a 6-week study in children 2 to 5 years of age with perennial allergic rhinitis, des-ciclesonide was detected in 41%, 22%, and 13% of the subjects treated with 200 mcg, 100 mcg, and 25 mcg ciclesonide nasal spray daily, respectively.

Drug-Drug Interactions: Based on *in vitro* studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by cytochrome P450 enzymes. The inhibitory potential of ciclesonide on cytochrome P450 isoenzymes has not been studied. *In vitro* studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a strong inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of the active metabolite of ciclesonide, des-ciclesonide, by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged.

In another drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults

and adolescents ≥ 12 years of age and children, 6 to 11 years of age, respectively, based on mcg/m^2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and adolescents ≥ 12 years of age and children, 6 to 11 years of age, respectively, based on mcg/m^2) in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings. No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2).

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies: Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily dose in adults based on mcg/m^2) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum daily intranasal dose in adults based on mcg/m^2) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m^2).

14 CLINICAL STUDIES

14.1 Seasonal and Perennial Allergic Rhinitis

Adults and Adolescent Patients 12 Years of Age and Older: The efficacy of OMNARIS Nasal Spray was evaluated in 3 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 to 6 weeks duration conducted in the United States and Canada in adolescents and adults with allergic rhinitis. The three trials included a total of 1524 patients (495 males and 1029 females) of whom 79 were adolescents, ages 12 to 17 years. The racial distribution in these three trials included 1374 Caucasians, 69 Blacks, 31 Asians, and 50 patients classified as Other. Of the 1524 patients, 546 patients received OMNARIS Nasal Spray 200 mcg once daily administered as 2 sprays in each nostril. Patients enrolled in the studies were 12 to 86 years of age with a history of seasonal or perennial allergic rhinitis, a positive skin test to at least one relevant allergen, and active symptoms of allergic rhinitis at study entry. Assessment of efficacy in these trials was based on patient recording of four nasal symptoms (runny nose, nasal itching, sneezing, and nasal congestion) on a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe) as reflective or instantaneous scores. Reflective scoring required the patients to record symptom severity over the previous 12 hours; the instantaneous scoring required patients to record symptom severity at the time of recording. The results of these trials showed that patients treated with OMNARIS Nasal Spray 200 mcg once daily exhibited statistically significantly greater decreases in total nasal symptom scores than placebo-treated patients. Secondary measures of efficacy were also generally supportive.

Dose-Ranging Trial: One of the three trials was a 2-week dose-ranging trial that evaluated efficacy of four doses of OMNARIS Nasal Spray in patients with seasonal allergic rhinitis. The primary efficacy endpoint was the difference from placebo in the change from

baseline of the sum of morning and evening reflective total nasal symptom score averaged over the 2-week treatment period. Results of the primary efficacy endpoint are shown in Table 3. In this trial OMNARIS Nasal Spray 200 mcg once daily was statistically significantly different from placebo, but the lower doses were not statistically significantly different from placebo.

Table 3 Mean change in reflective total nasal symptom score over 2 weeks in patients with seasonal allergic rhinitis

Treatment	N	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	144	18.8	-5.73	-1.35	(-2.43, -0.28)	0.014
Ciclesonide 100 mcg	145	18.7	-5.26	-0.88	(-1.96, 0.19)	0.11
Ciclesonide 50 mcg	143	18.4	-4.82	-0.44	(-1.52, 0.63)	0.42
Ciclesonide 25 mcg	146	18.7	-4.74	-0.35	(-1.42, 0.71)	0.51
Placebo	148	17.8	-4.38			

*Sum of AM and PM Scores; Maximum score = 24

** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline, day, and treatment by day interaction effects included in the model.

Seasonal Allergic Rhinitis Trial: The second trial was a 4-week single dose level trial conducted in patients with seasonal allergic rhinitis. The primary efficacy endpoint in the seasonal allergic rhinitis trial was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over the first 2 weeks of treatment. In this trial, OMNARIS Nasal Spray 200 mcg once daily was statistically significantly different from placebo (Table 4). Statistically significant differences in the morning pre-dose instantaneous total nasal symptom score indicate that the effect was maintained over the full 24-hour dosing interval.

Perennial Allergic Rhinitis Trial: The third trial was a 6-week single dose level trial conducted in patients with perennial allergic rhinitis. The primary efficacy endpoint in the perennial allergic rhinitis trial was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over the 6 weeks of treatment. In this trial, OMNARIS Nasal Spray 200 mcg once daily was statistically significantly different from placebo (Table 4). Statistically significant differences in the morning pre-dose instantaneous total nasal symptom score indicate that the effect was maintained over the full 24-hour dosing interval.

Table 4 Mean changes in reflective total nasal symptom score and instantaneous total nasal symptom score in allergic rhinitis trials

Treatment	N	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	162	8.96	-2.40	-0.90	(-1.36, -0.45)	<0.001
Placebo	162	8.83	-1.50			

Seasonal Allergic Rhinitis Trial – Instantaneous total nasal symptom score						
Ciclesonide 200 mcg	162	8.45	-1.87	-0.84	(-1.30, -0.39)	<0.001
Placebo	162	8.33	-1.03			
Perennial Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	232	7.59	-2.51	-0.62	(-0.97, -0.28)	<0.001
Placebo	229	7.72	-1.89			
Perennial Allergic Rhinitis Trial – Instantaneous total nasal symptom score						
Ciclesonide 200 mcg	232	7.05	-1.99	-0.53	(-0.90, -0.17)	0.004
Placebo	229	7.05	-1.46			

*Mean of AM and PM score from reflective total nasal symptom score; Mean of AM score for instantaneous total nasal symptom score; Maximum = 12

** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline, day, and treatment by day interaction effects included in the model.

Onset of action: Onset of action was evaluated in two environmental exposure unit studies in patients with seasonal allergic rhinitis receiving a single dose of OMNARIS Nasal Spray 200 mcg. Results from these two studies did not demonstrate a replicate onset of action within the assessment period. Onset of action was also evaluated in the 4-week seasonal allergic rhinitis and in the 6-week perennial allergic rhinitis trial by frequent recording of instantaneous symptom score after the first dose. In these trials, onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis.

Pediatric Patients Aged 6 to 11 Years: The efficacy of OMNARIS Nasal Spray was evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials in 1282 patients 6 to 11 years of age with allergic rhinitis. Of the two trials, one was 2 weeks in duration conducted in patients with seasonal allergic rhinitis that evaluated efficacy of 200 mcg and 100 mcg of OMNARIS Nasal Spray once daily. The other trial was 12 weeks in duration conducted in patients with perennial allergic rhinitis that evaluated efficacy of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray once daily. Of the total number of patients enrolled in the 2 studies, 380 were treated with 200 mcg of OMNARIS Nasal Spray once daily. The primary efficacy endpoint was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over 2 weeks of treatment in the seasonal allergic rhinitis trial and over the first 6 weeks of treatment in the perennial allergic rhinitis trial. In the 2-week trial in patients with seasonal allergic rhinitis, the OMNARIS Nasal Spray 200 mcg once daily dose was statistically significantly different from placebo, but the 100 mcg once daily dose was not statistically significantly different from placebo. The efficacy results for the seasonal allergic rhinitis trial are shown in Table 5.

Table 5 Mean changes in reflective total nasal symptom score in 1 seasonal allergic rhinitis trial in children 6 to 11 years of age

Treatment	N	Baseline*	Change from Baseline	Difference from Placebo**		
				Estimate	95% CI	p-value
Reflective total nasal symptom score						
Ciclesonide	215	8.25	-2.46	-0.39	(-0.76, -0.02)	0.040

200 mcg						
Ciclesonide 100 mcg	199	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo	204	8.41	-2.07			

*Mean of AM and PM score from reflective total nasal symptom score; Maximum = 12

** Estimates, 95% Confidence Intervals, and p-values were obtained from repeated measures ANCOVA analysis with treatment, baseline, day, and treatment by day interaction effects included in the model.

In the 12-week trial in patients with perennial allergic rhinitis, none of the ciclesonide doses were statistically significantly different from placebo. The means and 95% confidence intervals for the differences (OMNARIS Nasal Spray minus placebo) between OMNARIS Nasal Spray 200 mcg, 100 mcg, and 25 mcg treatment groups and placebo were -0.31 (-0.75, 0.13), 0.02 (-0.41, 0.46), and 0.09 (-0.35, 0.53), respectively.

Pediatric Patients Aged 2 to 5 Years: Efficacy of OMNARIS Nasal Spray in patients 2 to 5 years of age has not been established [see *Pediatric Use (8.4)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

OMNARIS is supplied in an amber glass bottle and provides for nasal delivery with a manual metered pump. OMNARIS Nasal Spray is supplied with an oxygen absorber sachet and enclosed in a foil pouch. The contents of one 12.5 gram bottle provide 120 actuations, after initial priming. Each spray delivers 50 mcg of ciclesonide from the nasal actuator. Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. The OMNARIS Nasal Spray bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after removal from the foil pouch either after 120 sprays following initial priming (since the amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled dose) or after 4 months. Patient instructions are also provided.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. Shake gently before use. Keep out of reach of children.

Omnaris Nasal Spray 50 mcg, 120 metered sprays; net fill weight 12.5 g.
NDC 63402-701-01

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling accompanying the product.

17.1 Local Nasal Effects

Patients should be informed that treatment with OMNARIS Nasal Spray may lead to adverse reactions, which include epistaxis and nasal ulceration. *Candida* infection may also occur with treatment with OMNARIS Nasal Spray. In addition, nasal corticosteroids are associated with nasal septal perforation and impaired wound healing. Avoid spraying OMNARIS Nasal Spray directly onto the nasal septum. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use OMNARIS Nasal Spray until healing has occurred [see *Warnings and Precautions (5.1)*].

17.2 Cataracts and Glaucoma

Patients should be informed that glaucoma and cataracts are associated with nasal and inhaled corticosteroid use. The patient should inform his/her health care provider if a change in vision is noted while using OMNARIS Nasal Spray [see *Warnings and Precautions (5.2)*].

17.3 Immunosuppression

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections, or ocular herpes simplex [see *Warnings and Precautions (5.3)*].

17.4 Use Daily

Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness depends on its regular use. In clinical trials, the onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be made during this time frame and periodically until the patient's symptoms are stabilized. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve by a reasonable time or if the condition worsens.

17.5 Keep Spray Out of Eyes

Patients should be informed to avoid spraying OMNARIS Nasal Spray in their eyes.

17.6 Storage and Handling

It is important that the bottle is gently shaken prior to use to ensure that a consistent amount is dispensed per actuation. The bottle should be discarded after 120 actuations following initial priming or after 4 months after the bottle is removed from the foil pouch, whichever occurs first.

SUNOVION

Manufactured for
Sunovion Pharmaceuticals Inc.
Marlborough MA 01752 USA
Made in Germany

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For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

October 2011
901379R02