OMNARIS®
(ciclesonide) Nasal Spray, 50 mcg
For intranasal use only

2009564

2009564

DESCRIPTION
The active component of OMNARIS® Nasal Spray is ciclesonide, a non-halogenated glucocorticoid. Ciclesonide is delivered as the R-epimer. The empirical formula is $C_{32}H_{44}O_7$ and its molecular weight is 540.7.

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 disodium; and hydrochloric acid to adjust the pH to 4.5. The contents of one 12.5 g bottle provide 120 actuations, after initial priming.

CLINICAL PHARMACOLOGY
Mechanism of Action
Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (desciclesonide or RM1) following intranasal application.

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.

Pharmacodynamics
In a 12-week study in children 6-11 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: Pharmacokinetics: Absorption).

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

Pharmacokinetics Absorption
Ciclesonide and desciclesonide 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.

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

Metabolism
Intranasal ciclesonide is hydrolyzed to a biologically active metabolite, desciclesonide, by esterases in the nasal mucosa. Desciclesonide 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 desciclesonide; 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 desciclesonide 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 desciclesonide are insufficient for pharmacokinetic calculations. However, population pharmacokinetic analysis showed that characteristics of desciclesonide after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject characteristics such as body weight, age, race, and gender. Compared to healthy subjects, the systemic exposure (C_{max} and AUC) in patients with liver impairment increased in the range of 1.4 to 2.7-fold after 1280 mcg ex-actuator ciclesonide by oral inhalation and dose adjustment in liver impairment is not necessary. Studies in renal impaired patients were not conducted.

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 children, 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 children, 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 vivo* 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).

INDICATIONS AND USAGE
Seasonal Allergic Rhinitis
OMNARIS® Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and adolescents 12 years of age and older.

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.

CONTRAINDICATIONS
OMNARIS® Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS
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. 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 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 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.

PRECAUTIONS
General
Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. Patients with a known hypersensitivity reaction to other corticosteroid preparations should use caution when using OMNARIS® Nasal Spray since cross reactivity to other corticosteroids including ciclesonide may also occur.

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. In clinical studies with OMNARIS® Nasal Spray, the development of localized infections of the nose and pharynx with Candida albicans has rarely 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. Intranasal 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.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

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 trials, 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. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients
Patients being treated with OMNARIS® Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to obtain medical advice. Patients should use OMNARIS® Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

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 timeframe and periodically until the patients' 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. For the proper use of this unit and to attain maximum improvement, the patients should read and follow the accompanying patient instructions carefully. Spraying OMNARIS® Nasal Spray directly into the eyes or onto the nasal septum should be avoided. 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. OMNARIS® Nasal Spray is supplied in an amber glass bottle. Patients should handle the glass bottle with care. OMNARIS® Nasal Spray should not be used if the pouch or the bottle is damaged or broken.

Drug Interactions
Based on *in vitro* studies in human liver microsomes, desciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by CYP450 enzymes. The inhibitory potential of ciclesonide on CYP450 isoenzymes has not been studied. *In vitro* studies demonstrated that the plasma protein binding of desciclesonide 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 erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either desciclesonide or erythromycin. In another drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of CYP450 3A4, increased the exposure (AUC) of desciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, the concomitant administration of potent inhibitors of CYP3A4 e.g. ketoconazole, itraconazole, HIV-protease inhibitors and cobicistat-containing products should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids. This is of limited importance for short term (1-2 weeks) treatment with CYP3A inhibitors, but should be taken into consideration during long-term treatment.

Pregnancy: Teratogenic Effects
Pregnancy Category C
Oral administration of ciclesonide in rats up to 900 mcg/kg (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 5 mcg/kg (less than the maximum human 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 based on mcg/m^2). There are no adequate and well-controlled studies in pregnant women.

OMNARIS® Nasal Spray, like other corticosteroids, 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.

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

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.

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 for the treatment of the symptoms of perennial allergic rhinitis in patients 6 to 11 years of age has not been established. The efficacy of OMNARIS® Nasal Spray in children 2 to 5 years of age has not been established. 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.

Clinical studies in children less than two years of age have not been conducted. Studies in children under 2 years of age are waived because of local and systemic safety concerns.

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). 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.

GERIATRIC USE
Clinical studies of OMNARIS® Nasal Spray did not include sufficient numbers of subjects age 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.

ADVERSE REACTIONS
Adult and Adolescent Patients Aged 12 Years and Older:
In controlled clinical studies conducted in the US and Canada, a total of 1,524 patients ages 12 years and older received treatment with ciclesonide administered intranasally. In studies of 2 to 6 weeks duration in patients 12 years and older, 546 patients were treated with OMNARIS® Nasal Spray 200 mcg daily, and in a study of up to one year in duration, 441 patients were treated with OMNARIS® Nasal Spray 200 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS® Nasal Spray was comparable to that in patients treated with placebo.

Adverse events 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 events; this rate was similar for patients treated with placebo. Table 1 displays adverse events, irrespective of drug relationship, 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

In a 52-week long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 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® Nasal Spray that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS® Nasal Spray versus placebo were epistaxis, nasal discomfort, and headache. No patient experienced a nasal septal perforation or nasal ulcer during long-term use of OMNARIS® Nasal Spray. While primarily designed to assess the long-term safety of OMNARIS® Nasal Spray 200 mcg once daily, this 52-week trial demonstrated greater decreases in total nasal symptom scores with OMNARIS® Nasal Spray versus placebo treated patients over the entire treatment period.

OVERDOSAGE
There are no data available on the effects of acute or chronic overdosage with OMNARIS® Nasal Spray. Because of low systemic bioavailability, acute overdosage is unlikely to require any therapy other than observation. 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. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION
Seasonal Allergic Rhinitis Adults and Adolescents (12 Years of Age and Older):
The recommended dose of OMNARIS® Nasal Spray is 200 mcg per day administered as 2 sprays (50 mcg/spray) in each nostril once daily.

Perennial Allergic Rhinitis Adults and Adolescents (12 Years of Age and Older):
The recommended dose of OMNARIS® Nasal Spray 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). 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. Once primed, each actuation of the pump delivers 50 mcg ciclesonide in a volume of 70 mcL from the nasal actuator.

HOW SUPPLIED (Storage condition)
OMNARIS® Nasal Spray 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. OMNARIS® Nasal Spray provides 120 metered sprays after initial priming. Each spray delivers 50 mcg of ciclesonide from the nasal actuator. The OMNARIS® Nasal Spray bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following priming (since the amount of ciclesonide delivered per spray thereafter maybe substantially less than the labeled dose) or 4 months after removal from the foil pouch, whichever comes first.
Store below 30°C. Do not freeze. Shake gently before use. Do not spray in eyes. Keep out of reach of children. Handle glass bottle with care. Do not use if pouch or bottle is damaged or broken.

OMNARIS® Nasal Spray 50 mcg, 120 metered sprays; net fill weight 12.5 g.

SHELF LIFE
Please refer to expiry date on outer carton.

Manufacturer
Contract Pharmaceuticals
Limited Canada, 7600 Danbro Crescent, Mississauga, ON, Canada L5N6L6

Date of Revision
January 2025

COVIS

COVIS

SGS Job No.:	7909949-4
Date:	11-09-25 14:00:30
SKU Number:	10001890
CMO Material Code:	2009564
Old CMO Material Code:	2008873
DWG Number:	AG16853_GA_30003_C_V02
Dimensions:	312mm x 480mm
Product Code:	N/A
Pharmacode:	N/A
Description:	OMNARIS FP NASAL SPRAY 50MCG BOTTLE 120P MYS_Leaflet
Created By:	DP

Printable Colours: Black

Non Print: Profile, Technical Info

SGS&CO

Bar prints 100mm @ 100%

Body text size	Smallest text size
7.5pt	7.5pt

COVIS

SGS Job No.:	7909949-4
Date:	11-09-25 14:00:30
SKU Number:	10001890
CMO Material Code:	2009564
Old CMO Material Code:	2008873
DWG Number:	AG16853_GA_30003_C_V02
Dimensions:	312mm x 480mm
Product Code:	N/A
Pharmacode:	N/A
Description:	OMNARIS FP NASAL SPRAY 50MCG BOTTLE 120P MYS_Leaflet
Created By:	DP

Printable Colours:

Black

Non Print:

Profile

Technical Info

SGS&CO

Bar prints 100mm @ 100%

Body text size	Smallest text size
7.5pt	7.5pt