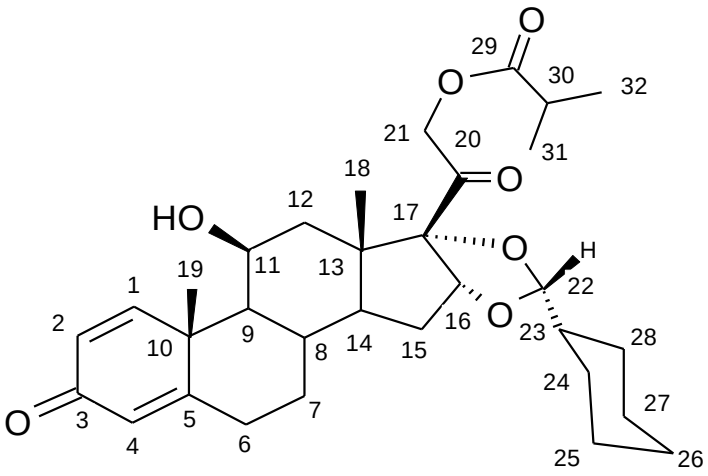
OMNARIS® NASAL SPRAY

PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient:	Ciclesonide
Chemical name (CAS):	pregna-1,4-diene-3,20-dione,16,17-[[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α)-
Molecular formula:	$C_{32}H_{44}O_7$
CAS Number:	126544-47-6 (as the R-epimer)
Molecular weight:	540.7
Structural formula:	



DESCRIPTION

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 cellulose microcrystalline, carmellose sodium, hypromellose, potassium sorbate, disodium edetate, hydrochloric acid to adjust the pH to 4.5, and purified water. The contents of one 15 mL or 10 mL bottle provide 120 actuations or 60 actuations, respectively, after initial priming (see DOSAGE AND ADMINISTRATION). Once primed, each actuation of the pump delivers 50 µg ciclesonide in a volume of 70 µL from the nasal actuator.

PHARMACOLOGY

Mechanism of Action

Ciclesonide is a pro-drug that is enzymatically hydrolysed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide) 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.

The anti-inflammatory properties of ciclesonide and des-ciclesonide 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.

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 µg of ciclesonide nasal spray daily, the peak serum concentrations of des-ciclesonide in all subjects were found to be below 30 pg/mL. Of those treated with 800 µg and 400 µg daily, 100% and 67% had detectable levels of des-ciclesonide, respectively. With daily doses of 200 µg 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 Cmax was less than 10 pg/mL and 602 pg/mL following a single dose of ciclesonide nasal spray (300 µg) and orally inhaled ciclesonide (320 µg, Alvesco), respectively.

In paediatric subjects treated with 25 to 200 µg 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 µg and in 5% of those treated with 100 µg ciclesonide nasal spray daily.

Distribution

Following intravenous administration of 800 µg 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 approximately 1% of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

Metabolism

Intranasal ciclesonide is hydrolysed to a biologically active metabolite des-ciclesonide by esterases in the nasal mucosa. 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 characterised. 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.

Excretion

Following intravenous administration of 800 µg of ciclesonide, the clearance values of ciclesonide and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively). ^{14}C-labelled ciclesonide was predominantly excreted via the faeces 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.

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

Pharmacodynamics

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 µg daily of ciclesonide for 14 days. In a 1 year safety study including 174 patients treated with ciclesonide 200 µg once daily 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.

In two studies conducted in children with perennial allergic rhinitis, daily doses of 200 µg, 100 µg, and 25 µg of ciclesonide were compared to placebo nasal spray. The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary free cortisol compared to the placebo group. In the 12-week study in children 6-11 years of age, the difference (and 95% confidence intervals) from placebo in the

mean change from baseline to 12 weeks was -0.81 (-4.0, 2.4) µg/day for the 200 µg dose group. The mean morning plasma cortisol value did not show any consistent treatment effect. In the 6-week study in children 2-5 years of age, the difference (and 95% confidence intervals) from placebo in the mean change from baseline to 6 weeks was -2.04 (-4.4, 0.3) µg/day for the 200 µg dose groups. The plasma cortisol decreased numerically after treatment with ciclesonide with the difference (and 95% confidence intervals) from placebo in the mean change in plasma cortisol from baseline to 6 weeks being -1.04 (-2.7, 0.7) µg/dL for the 200 µg dose group. In the studies, serum was assayed for ciclesonide and des-ciclesonide (see PHARMACOLOGY: Pharmacokinetics: Absorption).

CLINICAL TRIALS

Seasonal Allergic Rhinitis and Perennial Allergic Rhinitis

Adult and Adolescent Patients Aged 12 Years and Older

The efficacy and safety of OMNARIS were evaluated in 4 randomised, double-blind, parallel-group, multi-centre, placebo-controlled clinical trials of 2 weeks to 1 year in duration conducted in adults and adolescents with allergic rhinitis. Three of these trials were 2 to 6 weeks in duration and primarily designed to assess efficacy. One of these trials was 1 year in duration and primarily designed to assess safety. The three trials of 2 to 6 weeks duration included a total of 1524 patients (495 males and 1029 females) of whom 79 were adolescents, ages 12 to 17 years. Of the 1524 patients, 546 patients received OMNARIS 200 µg once daily. 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 200 µg once daily exhibited statistically significantly greater decreases in total nasal symptom scores than placebo-treated patients. Secondary measures of efficacy were generally supportive.

In the 2-week dose-ranging trial that evaluated efficacy of OMNARIS 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. In this trial OMNARIS 200 µg once daily was statistically significantly different from placebo.

In the 4-week single dose-level trial conducted in patients with seasonal allergic rhinitis and the 6-week single dose-level trial conducted in patients with perennial allergic rhinitis, the primary efficacy endpoints were 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 and over the 6 weeks of treatment, respectively. In these trials, OMNARIS 200 µg once daily was

statistically significantly different from placebo. 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.

Results of the primary efficacy endpoint in these trials are shown in Table 1.

Table 1 Mean changes in reflective and instantaneous total nasal symptom scores (TNSS) in seasonal and perennial allergic rhinitis trials

Study	Treatment	N	Duration of Study	Change from Baseline*	Difference from Placebo		
					Mean	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective TNSS							
TBN-CL-002	Ciclesonide 200 µg	144	2 weeks	-5.73	-1.35	(-2.43, -0.28)	0.014
	Placebo	148	2 weeks	-4.38			
Seasonal Allergic Rhinitis Trial – Reflective TNSS							
M1-401	Ciclesonide 200 µg	162	4 weeks	-2.40	-0.90	(-1.36, -0.45)	<0.001
	Placebo	162	4 weeks	-1.50			
Seasonal Allergic Rhinitis Trial – Instantaneous TNSS							
M1-401	Ciclesonide 200 µg	162	4 weeks	-1.87	-0.84	(-1.30, -0.39)	<0.001
	Placebo	162	4 weeks	-1.03			
Perennial Allergic Rhinitis Trial – Reflective TNSS							
M1-402	Ciclesonide 200 µg	232	6 weeks	-2.51	-0.62	(-0.97, -0.28)	<0.001
	Placebo	229	6 weeks	-1.89			
Perennial Allergic Rhinitis Trial – Instantaneous TNSS							
M1-402	Ciclesonide 200 µg	232	6 weeks	-1.99	-0.53	(-0.90, -0.17)	0.004
	Placebo	229	6 weeks	-1.46			

* Baseline: Mean of morning and evening score from reflective TNSS; Mean of morning and evening score from instantaneous TNSS; Maximum score = 12.

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 24-hour reflective total nasal symptom score from baseline was greater in the treatment group versus placebo ($p<0.001$) with no evidence of tachyphylaxis.

Onset of action was evaluated in two environmental exposure unit studies with a single dose of OMNARIS 200 µg. 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.

Paediatric Patients Aged 6 to 11 Years

The efficacy of OMNARIS was evaluated in 618 children aged 6 to 11 years old with seasonal allergic rhinitis in a randomised, double-blind, parallel-group, multi-centre, placebo-controlled clinical trial. The 2-week trial conducted in patients compared the efficacy of ciclesonide 200 µg and 100 µg once daily nasal spray. 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 study, the ciclesonide 200 µg once daily dose was statistically significantly different from placebo, but the 100 µg once daily dose was not statistically significantly different from placebo. The efficacy results for the seasonal allergic rhinitis trial are shown in Table 2.

Table 2 Mean changes in reflective and instantaneous total nasal symptom scores (TNSS) in the seasonal allergic rhinitis trial in children 6 to 11 years of age

Study	Treatment	N	Duration of Study	Change from Baseline*	Difference from Placebo		
					Mean	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective TNSS							
M1-417	Ciclesonide 200 µg	215	2 weeks	-2.46	-0.39	(-0.76, -0.02)	0.040
	Placebo	204	2 weeks	-2.07			
Seasonal Allergic Rhinitis Trial – Instantaneous TNSS							
M1-417	Ciclesonide 200 µg	215	2 weeks	-2.24	-0.37	(-0.73, 0.00)	0.047
	Placebo	204	2 weeks	-1.87			

* Baseline: Mean of morning and evening score from reflective TNSS; Mean of morning and evening score from instantaneous TNSS; Maximum score = 12.

INDICATIONS

OMNARIS Nasal Spray is indicated for:

- the treatment of seasonal allergic rhinitis in adults and children 6 years of age and older.
- the treatment of perennial allergic rhinitis in adults and adolescents 12 years of age and older.

CONTRAINDICATIONS

Patients with a hypersensitivity to ciclesonide or any of its ingredients.

PRECAUTIONS

Immune System

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 ciclesonide nasal spray since cross reactivity to other corticosteroids including ciclesonide may also occur. 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 have not been properly immunised, 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.

Local Nasal Effects

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 localised 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 corticosteroid. 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.

Corticosteroid 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.

Systemic Effects

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 ciclesonide 200 µg daily for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed between ciclesonide- and placebo-treated patients. Additionally, no significant differences between the two patient groups 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.

Intranasal corticosteroids may cause a reduction in growth velocity when administered to paediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route (see PRECAUTIONS: Paediatric Use).

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. 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.

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.

Effects on Fertility

No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally with ciclesonide at up to 900 µg/kg/day (approximately 41 times the maximum human daily intranasal dose in adults based on µg/m^2 body surface area in a 50 kg adult).

Use in Pregnancy (Category B3)

No adverse effects on embryofoetal development were observed in rats treated with ciclesonide at oral doses up to 900 µg/kg/day (41 times the maximum human daily intranasal dose in adults on a body surface area basis) during the period of organogenesis. In a study in rats in which this dose was administered throughout gestation and lactation, pup birth weight and postnatal body weight gain were reduced; this occurred in the context of maternotoxicity. In rabbits, adverse effects on embryofoetal development occurred at subcutaneous doses ≥5 µg/kg/day (0.6 times the maximum adult human dose based on body surface area), and comprised cleft palate, fore and/or hind leg flexure, enlarged fontanelle, incomplete ossification of skull bones, parchment-like skin and decreased foetal weight. Ciclesonide increased foetal loss in the rabbit with subcutaneous administration at doses ≥100 µg/kg/day (11 times the maximum adult human dose based on body surface area).

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, foetus or infant. Infants born to mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

Use in Lactation

It is unknown if ciclesonide is excreted in human milk. There was limited excretion of ciclesonide and/or its metabolites in to milk in lactating rats after intravenous or oral administration. Oral administration of ciclesonide to rats from early pregnancy until weaning was associated with reduced body weight in pups (see Use in Pregnancy). 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.

Paediatric Use

The efficacy of OMNARIS in children 6 years of age and older for the treatment of the symptoms of allergic rhinitis is supported by evidence from four adequate and well-controlled studies in adults and adolescents 12 years of age and older with seasonal or perennial allergic rhinitis and one study in patients 6 to 11 years of age with seasonal allergic rhinitis (see CLINICAL TRIALS). The efficacy of OMNARIS in children under 5 years of age has not been established. The safety of OMNARIS in children 2 to 11 years of age was evaluated in four controlled clinical studies of 2 to 12 weeks duration (see PHARMACOLOGY: Pharmacodynamics, and CLINICAL TRIALS).The growth of paediatric patients receiving intranasal corticosteroids, including OMNARIS, 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 non-corticosteroid treatment alternatives. To minimise the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms (see PRECAUTIONS: Systemic Effects, and ADVERSE EFFECTS).

Use in the Elderly

A total of 31 patients above 65 years of age (age range 65 to 75 years) have been treated with OMNARIS 200 µg/day for up to one 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.

Genotoxicity

Ciclesonide did not induce gene mutations in bacterial (Ames) or mammalian (HPRT) tests in vitro, nor induce chromosomal aberrations in human lymphocytes or micronuclei in Chinese hamster V79 cells in vitro. Racemic ciclesonide was also negative in the Ames test. In contrast, ciclesonide induced micronuclei in mouse bone marrow in vivo (at ≥75 mg/kg in females and >1000 mg/kg in males). Positive in vivo clastogenicity results have also been observed with high doses of other corticosteroids and may reflect effects on erythrocyte differentiation. The clinical relevance of these clastogenicity findings is unknown but likely limited.

Carcinogenicity

The carcinogenic potential of ciclesonide was investigated in a 2-year oral study in mice and in a 2-year inhalation study in rats. Gastric adenomas (benign tumour) were significantly increased in female mice at 900 µg/kg/day (approximately 20 and 11 times the maximum human daily intranasal dose in adults and children, respectively, based on µg/m^2 body surface area).

This effect may arise from a local action in the stomach, with local exposure (based on µg/kg doses being ≥90 times higher in the animals compared with humans receiving the maximum recommended dose of OMNARIS. No tumourigenicity was observed in rats administered ciclesonide by inhalation at up to 89 µg/kg/day (males) or 104 µg/kg/day (females) (approximately 4 and 2 times the maximum human dose in adults and children, respectively, based on body surface area).

Effects on Laboratory Tests

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

INTERACTIONS WITH OTHER MEDICINES

Based on *in vitro* studies in human liver microsomes and hepatocytes, des-ciclesonide is not an inhibitor of CYP isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 at therapeutic concentrations, and ciclesonide is not an inducer of CYP1A2, 2C9 2C19 or 3A4. The inhibitory potential of ciclesonide on CYP450 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 that protein binding-based drug interactions are unlikely.

In vitro data indicate that CYP 3A4 is the major enzyme involved in the metabolism of the active metabolite, des-ciclesonide, in man. A drug interaction study with orally inhaled ciclesonide and oral erythromycin, a substrate and weak inhibitor of CYP 3A4, had no relevant effect on the pharmacokinetics of either des-ciclesonide or erythromycin. In another drug interaction study at steady-state with orally inhaled ciclesonide and oral ketoconazole, a potent CYP 3A4 inhibitor, the exposure (AUC) of des-ciclesonide increased by approximately 3.5-fold, while levels of ciclesonide remained unchanged.

The serum levels of ciclesonide and des-ciclesonide 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 CYP 3A4 (e.g. protease inhibitors for the treatment of HIV infections) should be considered with caution because there might be an increase in systemic drug levels of des-ciclesonide.

ADVERSE EFFECTS

In controlled clinical studies with patients receiving ciclesonide aqueous nasal spray, the overall incidence of adverse events for patients treated with ciclesonide aqueous

nasal spray was comparable to that in patients treated with placebo. Adverse reactions reported at an incidence of 1% or greater and more commonly reported in ciclesonide aqueous nasal spray versus placebo were as follows:

Nervous system disorders: headache

Respiratory, thoracic and mediastinal disorders: nasopharyngitis, epistaxis, sinusitis.

Adult and Adolescent Patients Aged 12 Years and Older

In controlled clinical studies, a total of 1524 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 200 µg daily, and in a study of up to one year in duration, 441 patients were treated with OMNARIS 200 µg daily. The overall incidence of adverse events for patients treated with OMNARIS 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 in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo. Table 3 displays adverse events, irrespective of drug relationship, that occurred with an incidence of 2% or greater and more frequently with OMNARIS than with placebo in clinical trials of 2 to 6 weeks in duration.

Table 3 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 200 µg 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 that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS versus placebo were epistaxis, nasal discomfort, and headache. 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.

Less common adverse reactions reported in controlled clinical trials 2 to 52 weeks in duration in patients 12 years of age and older with seasonal or perennial allergic rhinitis were:

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

Infections and infestations: candidiasis (0.2%), rhinitis (0.2%)

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

Nervous system disorders: dysgeusia (0.2%)

Respiratory, thoracic and mediastinal disorders: nasal dryness (0.4%), pharyngolaryngeal pain (0.4%), rhinorrhoea* (0.3%), nasal septum disorder (0.2%), throat irritation* (0.2%)

* *Occurred at rates ≤placebo*

Paediatric Patients Aged 6 to 11 Years

Two controlled clinical studies 2 and 12 weeks in duration were conducted in a total of 1282 patients with allergic rhinitis ages 6 to 11 years, of which 913 were treated with OMNARIS 200 µg, 100 µg or 25 µg daily. The overall incidence of adverse events for patients treated with OMNARIS was comparable to that in patients treated with placebo. 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 200 µg or 100 µg, respectively, discontinued because of adverse events; these rates were lower than the rate in patients treated with placebo (2.8%). Table 4 displays adverse events, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS 200 µg than with placebo.

Table 4 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 200 µg Once Daily (n = 380), %	Placebo (n = 369), %
Headache	6.6	5.7
Nasopharyngitis	6.6	5.4
Pharyngolaryngeal Pain	3.4	3.3

The effect of orally inhaled ciclesonide (Alvesco) on growth in 609 children aged 5 to 9 years was investigated in a placebo-controlled multi-center, double-blind, randomised parallel-group study of 12 months duration. In the modified intention-to-treat (mITT) analysis, the mean growth velocities observed during the double-blind treatment period were 5.76 cm/year in the placebo group, 5.75 cm/year in the 40 µg ciclesonide group, and 5.60 cm/year in the 160 µg ciclesonide group. It can be concluded that doses of ciclesonide administered at 40 µg or 160 µg once daily were non-inferior to placebo with respect to growth velocity. In addition, no significant difference was observed between ciclesonide and placebo as measured by 24-hour urinary free cortisol in 292 patients who were studied for HPA axis function.

These effects described above were observed with ciclesonide administered as a metered dose inhaler utilising a different formulation and at different dosages to OMNARIS.

Post-marketing Experience

Hypersensitivity reactions, including angioedema, loss of consciousness, nasal oedema, dyspnoea, and nasal septum perforation have been reported in association with post-market use of OMNARIS. Because these reactions are reported voluntarily

from a population of uncertain size and are not always confirmed with a health care professional, it is not possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

DOSAGE AND ADMINISTRATION

OMNARIS should only be administered by the intranasal route.

Dosage Consideration

The recommended dose of OMNARIS is 200 µg per day administered as 2 actuations (50 µg/actuation) in each nostril once daily.

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

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 actuation or until a fine mist appears.

During dosing, users are advised to tilt the head forward slightly and, while keeping the bottle upright, users are advised to press the pump quickly and firmly and inhale through the nose as they spray.

OVERDOSAGE

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

Further information for advice on management can also be obtained from the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Each pack of OMNARIS contains one spray pump bottle containing 120 or 60 actuations of 50 µg/actuation of ciclesonide.

Store below 30°C. Do not freeze.

Store in the foil pouch and only open pouch immediately before first use. Discard 4 months after first opening of pouch.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

16 December 2011

DATE OF MOST RECENT AMENDMENT

23 September 2016