Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ciclesonide

Proprietary Product Name: Omnaris

Sponsor: Nycomed Pty Ltd

January 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	New Dose Form, New Route of Administration, Extension of Indications
Decision:	Approved
Date of Initial Decision:	Rejected: 12 July 2011
Date of Final Decision:	Approved: 28 November 2011
Active ingredient(s):	Ciclesonide
Product Name(s):	Omnaris
Sponsor's Name and Address:	Nycomed Pty Ltd 2 Lyon Park Road North Ryde NSW 2113
Dose form(s):	Nasal spay
Strength(s):	50 µg per actuation
Container(s):	Bottle
Pack size(s):	60 and 120 actuations
Approved Therapeutic use:	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.
Route(s) of administration:	Nasal
Dosage:	200 µg daily
ARTG Number:	167910

Product Background

Currently, ciclesonide is a glucocorticoid which is available in Australia as Alvesco containing ciclesonide 40, 80 and 160 µg per actuation aerosol can. Alvesco was approved for registration in Australia as of February 2004 for the prophylactic treatment of asthma in adults and adolescents. Alvesco was approved for use in children 6 years of age and older in 2008.

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

The precise mechanism by which ciclesonide affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (for example, mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (for example, histamine, eicosanoids, leukotrienes and cytokines) involved in allergic inflammation. The antiinflammatory 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.

The sponsor claims that ciclesonide, when administered intranasally, shows negligible absorption into the systemic circulation. The liver is the main site of systemic metabolism and inactivation of ciclesonide and the active metabolite. The main enzyme for metabolism is the cytochrome P450 isoenzyme 3A4 (CYP3A4).

The sponsor also claims that the proposed nasal spray formulation delivers droplets in a size range with the 10% and 90% limits of the size distribution of approximately 17 and 147 µm (diameter), respectively. With this size spectrum, intranasal administration of ciclesonide is expected to have negligible access to the lower airways.

This AusPAR describes the evaluation of an application by Nycomed Pty Ltd (the sponsor) to extend the indications for ciclesonide to include treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in a new dosage form with a new route of administration.

The currently approved indications and dosage recommendations are:

Alvesco is indicated as prophylactic treatment of asthma in adults, adolescents and in children 6 years of age and older.

Dosing recommendation for adults and adolescents 12 years of age and older: The recommended dose range is 80 to 320 µg per day in adult and adolescent patients. In certain circumstances the dosage may be increased in adults (see below). Patients should be given a starting dose of Alvesco which is appropriate to the severity of their disease. Typical starting doses in patients either newly diagnosed or not previously treated with inhaled corticosteroids are:

Mild asthma: 160 µg once daily
Moderate asthma: 160-320 µg once daily
Severe asthma: 320 µg once daily. In certain circumstances in adult patients, this may be increased to 640 µg daily, administered as 320 µg twice daily (see below).

Patients previously maintained on another inhaled corticosteroid may require a higher dose depending on their current maintenance dose. Alvesco can be administered as 1 or 2 puffs once daily either in the morning or evening. In the case of a higher dose, twice daily administration is recommended (see below). The dose should be adjusted to the lowest dose at which effective control of asthma is maintained.

Adult Patients:

Higher doses in certain circumstances: Adults with severe asthma may have their daily dose increased from 320 µg once daily to 320 µg twice daily. However, the superiority of this higher dose versus 320 µg once daily has not been unequivocally established. The dose should be adjusted to the lowest dose at which effective control of asthma is maintained.

Dosing recommendation for children (6 to 11 years): The recommended dose of Alvesco for children is 80 or 160 µg once daily. Alvesco can be administered as 1 or 2 puffs once daily either in the morning or evening. The use of a spacer is recommended for children 6 to 11 years.

The proposed indications and dosage recommendations for Omnaris are:

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.

The recommended dose of Omnaris is 200 µg per day administered as 2 sprays (50 µg/spray) in each nostril once daily. The maximum total daily dosage should not exceed 2 sprays in each nostril (200 µg/day).

Regulatory Status

A similar application was approved in the US on 20 October 2006 and Canada on 10 December 2007. An application was submitted in New Zealand in May 2010.

Product Information

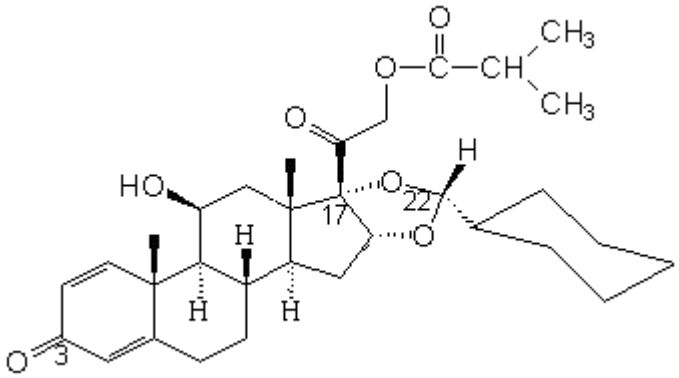
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Alvesco containing ciclesonide 40, 80 and 160 µg pressurised metered dose oral inhalations are currently registered by the sponsor for use in the treatment of asthma.

Ciclesonide is a steroidal prodrug which is closely related structurally to budesonide. Ciclesonide contains 9 chiral centres but is presented as a single enantiomer (that is, with stereochemical purity at 22*R* epimer; compared with budesonide which is an epimeric mixture at Position 22).

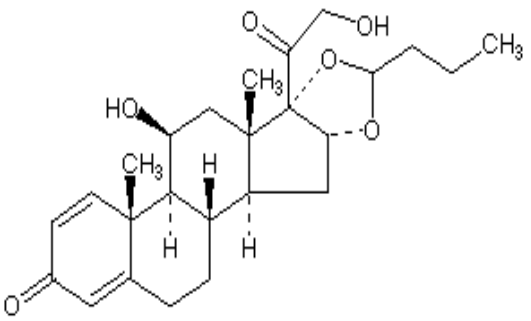


$C_{32}H_{44}O_7$

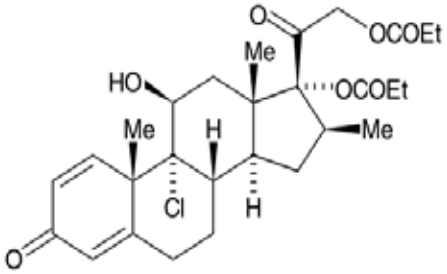
MW 540.7

Company code: B9207-015

ciclesonide



budesonide



beclomethasone dipropionate

Ciclesonide is practically insoluble in water (approximately 0.2 mg/L). It is not the subject of a pharmacopoeial monograph. The drug is stable on storage. Control of the drug substance was considered acceptable.

Drug Product

The proposed liquid spray is a white hypotonic aqueous suspension containing the drug. Omnaris Nasal Spray also contains microcrystalline cellulose, carmellose sodium, hypromellose, potassium sorbate, disodium edetate, hydrochloric acid to adjust the pH to 4.5 and purified water. The preservative efficacy is acceptable in simulated use.

Two presentations are proposed, delivering a minimum of 60 or 120 actuations. The formulation is identical for both. The suspension is filled into amber glass bottles and fitted with a metering, atomising spray pump. The suspension is manually pumped to atomise through a nozzle orifice. There is overfill to allow for priming and to ensure delivery of the labelled number of sprays. There is no dose counter but the level of remaining suspension can apparently be seen by the user via a 'window' on the bottle.

The same formulation has been used throughout clinical development, except for variation of the drug substance concentration (between 12.5 - 100 µg/actuation). The proposed commercial formulation (50 µg/actuation) was used in all Phase III clinical studies.

The chemistry and quality control aspects of the finished product were acceptable.

Biopharmaceutics

Ciclesonide is a prodrug, cleaved by esterases to the active metabolite "RM1" or 'B9207-021'. It is claimed that drug is more strongly bound to plasma proteins than budesonide or fluticasone "thus reducing the potential for systemic glucocorticoid effects". Ciclesonide apparently does not epimerise *in vivo*. The oral bioavailability is < 1 %.

Omnaris acts locally. Bioavailability data are reviewed as one measure of safety; the application also includes cortisol suppression data. One bioavailability study was submitted which provides data on the extent of systemic absorption:

Study 468/2007: *A Randomized, Open Label, Single Dose, Three Period Crossover, Pharmacokinetic Study Designed to Compare the Systemic Des-Ciclesonide Exposure of Omnaris (Ciclesonide) Nasal Spray, Ciclesonide HFA Nasal Aerosol, and Orally Inhaled Ciclesonide.* This was a three way crossover comparison of single doses in 29 healthy volunteers with washout periods from 7 up to 14 days between treatments of:

- A: ciclesonide 300 µg (6x50 µg) intranasal Omnaris aqueous nasal spray (proposed)
- B: ciclesonide 300 µg (4x75 µg) intranasal via pressurised metered nasal inhaler
- C: ciclesonide 320 µg (4x80 µg) Alvesco pressurised metered dose inhaler

No ciclesonide concentrations could be detected following supratherapeutic doses of intranasal administration of ciclesonide aqueous nasal spray. (Ciclesonide was measurable following the other treatments.) Levels of the RM1 metabolite were also low after the aqueous nasal spray doses, with quantified levels seen in only 5 subjects. While the sponsor attempted some statistical analysis, it is only prudent to conclude that systemic ciclesonide exposure is low relative to similar pressurised metered dose inhaler doses (Alvesco).

Spray delivery from Omnaris is not significantly affected by the angle of the bottle. However, the relative angle of a nasal spray bottle and nose during dosing can reportedly

affect nasal drug delivery.[1] In clinical trials, instructions were to use the spray with the bottle upright. The proposed Product Information (PI) recommends use with the head tilted slightly forward.

Advisory Committee Considerations

The application was considered at the 136th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC made a recommendation in relation to the Consumer Medicine Information (CMI) which is beyond the scope of this AusPAR.

Quality Summary and Conclusions

There were no outstanding chemistry and quality control issues. Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical Findings

Introduction

Nonclinical data comprised information previously submitted to support the registration of Alvesco, as well as new studies on pharmacology, pharmacokinetics, repeat dose toxicity and local tolerance, which are the focus of this report.

Pharmacology

Ciclesonide is a glucocorticosteroid. It is enzymatically hydrolysed to an active and more potent metabolite, C21-desisobutyryl-ciclesonide (designated RM1 in this report).

Of relevance to the proposed new indication, ciclesonide was shown to inhibit IL-1β-induced IL-8 production by human nasal epithelial cells *in vitro* (median effective concentration [EC_{50}], 0.81 nM) and to produce significant and long lasting inhibition of allergen induced nasal blockage and eosinophil infiltration *in vivo* in sensitised guinea pigs (0.1–10 µg/nostril; assessment to 6–7 hours [h] post dose). An *in vitro* pharmacodynamic interaction study suggested synergistic effects of ciclesonide and an H1-histamine receptor antagonist (azelastine) to inhibit lipopolysaccharide induced cytokine release from human monocytes, although the enhancement was not statistically significant and not also evident with RM1 and azelastine in combination.

Pharmacokinetics

Like bronchial and alveolar epithelial cells and hepatocytes, human nasal epithelial cells and animal nasal mucosal homogenates were shown to metabolise ciclesonide to RM1 *in vitro*. This was chiefly mediated by carboxylesterases, with a lesser contribution by cholinesterases. Fatty acid conjugation of RM1 by human nasal epithelial cells *in vitro* and by rabbit nasal mucosa *in vivo* was observed, as seen previously in rat lung.

Very limited systemic absorption of ciclesonide following intranasal administration was evident in rats, dogs and humans. Comparative clinical studies revealed substantially lower peak serum levels of RM1 in children and adults following administration of ciclesonide by the nasal route compared with by oral inhalation (>7–14 times at the maximum recommended human dose [MRHD] of 200 µg/day.)

In other newly submitted pharmacokinetic studies, plasma/serum protein binding by ciclesonide and RM1 was found to be high (and similar) in humans and laboratory animal species. Protein binding by RM1 in human plasma was not affected by the presence of

[1] Foo MY et al. J Aerosol Med 2007; 20: 495.

warfarin or salicylic acid. Some time dependent distribution of ^{14}C-ciclesonide derived radioactivity to red blood cells was evident in mice and rats, while distribution to red blood cells was limited in non-rodent species, including humans. RM1 had no significant inhibitory activity against human CYPs 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 (median inhibitory concentration [IC_{50}] values, >3 µM), and ciclesonide (≤1 µM) did not induce CYPs 1A2, 2C9, 2C19 or 3A4 in cultures of human hepatocytes.

Toxicology

Good Laboratory Practice compliant repeat dose toxicity studies of up to 4 weeks duration were conducted in rats and 26 weeks in dogs using the clinical route (intranasal). Doses were administered more frequently and/or at higher strengths than is proposed clinically (that is, up to 12 times daily per nostril at 200 µg/actuation in dogs). Two new studies in juvenile rats, involving inhalational administration for up to 13 weeks, were also submitted.

Relative exposure

In clinical studies, ciclesonide was undetectable and the active metabolite RM1 was below or peaked near its lowest limit of quantification in serum from adult and paediatric subjects receiving the nasal spray at the recommended dose. As such, human area under the plasma concentration time curve (AUC) values were not determined. Animal:human exposure ratios achieved in the intranasal repeat dose toxicity studies have therefore been calculated based on comparisons of µg/kg doses for consideration of local effects and µg/m^2 body surface area doses for consideration of systemic effects. Very large local and systemic exposure multiples were obtained in the intranasal studies (Table 1).

Table 1: Relative exposure in repeat-dose toxicity studies [intranasal administration]

Study	Species; treatment duration		Dose		Relative exposure			
			µg/kg/day	µg/m^2/day	local [based on µg/kg/day]		systemic [based on µg/m^2/day]	
					adult	child	adult	child
218/2001, 221/2001, 49/2003	**Rat** (Wistar)	2–4 weeks	107	642	27	11	5	2.6
			214	1284	54	21	10	5
			429	2574	107	43	20	10
219/2001, 16/2002	**Dog** (Beagle)	2–4 weeks	120	2400	30	12	18	10
			240	4800	60	24	36	19
			480	9600	120	48	73	38
103/2004		26 weeks	25	500	6	2.5	4	2
			100	2000	25	10	15	8
			400	8000	100	40	61	32
Human; Omnaris MRHD, 200 µg/day		adult	4	132	–	–	–	–
		child	10	250	–	–	–	–

Factors used to convert µg/kg to µg/m^2 doses in rats, dogs, human adults (50 kg) and children (20 kg; 6 years old) are 6, 20, 33 and 25, respectively; MRHD = maximum recommended human dose; – = not applicable.

Local effects

Intranasal administration of the ciclesonide spray was well tolerated locally in rats and dogs, with no evidence of irritation of the nasal mucosa or other respiratory tract tissues observed in any of the studies. Local treatment related findings were limited to atrophy of the mucosal associated lymphoid tissue of the nasal cavity and decreased number of goblet cells in the trachea of dogs (seen at ≥240 and 400 µg/kg/day, respectively). These effects were minimal and at most slight in severity, respectively, reversible upon treatment withdrawal and consistent with corticosteroid activity. No Observable Effect Levels (NOELs) for these effects were 429 µg/kg/day in the rat (4 week study; relative exposure: 43 and 107 times the exposure expected in children and adults, respectively) and 100 µg/kg/day in the dog (6 month study; relative exposure: 10 and 25 times the exposure expected in children and adults, respectively).

The ciclesonide nasal spray was also found not to be an ocular irritant in a specialised study in rabbits.

Systemic effects

Major systemic findings in the intranasal studies comprised suppression of bodyweight gain and thymic and adrenal cortical atrophy. In the pivotal studies, systemic toxicity was evident at the high dose levels only (429 µg/kg/day in rats and 400 µg/kg/day in dogs). The effects were reversible and are consistent with corticosteroid activity. There were no significant systemic effects in rats treated with the nasal spray at 214 µg/kg/day for 4 weeks (relative exposure: 5 and 10 times the exposure expected in children and adults, respectively) or in dogs treated at 100 µg/kg/day for 6 months (relative exposure: 8 and 15 times the exposure expected in children and adults, respectively).

Carcinogenicity

Carcinogenicity studies by the intranasal route were not conducted. This was acceptable considering the existing data (2 year oral and inhalational studies in mice and rats, respectively) and the absence of proliferative or pre-neoplastic changes in the nasal cavity and other upper respiratory tract tissues in the repeat dose toxicity studies.

Paediatric use

No studies by the intranasal route were conducted in juvenile animals. This was acceptable given that ciclesonide is already approved for use in the paediatric population (≥6 years old), that systemic exposure with use of Omnaris will be considerably lower compared with Alvesco and given the high local tolerability of the nasal spray evident in the general studies, conducted in young adult animals.

Newly submitted studies in juvenile rats treated with ciclesonide (metered dose inhaler formulation) by the inhalational route revealed atrophy of the adrenal and thymus glands, thymic lymphoid depletion, effects on mammary gland development (increased glandular secretion in males and lobular hypertrophy/hyperplasia in females) and various changes in clinical chemistry indicative of altered renal function. These findings were also observed in previously evaluated inhalational studies in adult animals and reflect pharmacologically mediated effects.

Nonclinical Summary and Conclusions

Ciclesonide is a glucocorticosteroid with a major pharmacologically active metabolite (des-ciclesonide; RM1). Supporting use for the proposed indication, ciclesonide was shown to inhibit cytokine release by human nasal epithelial cells *in vitro* and to produce significant and long lasting inhibition of nasal blockage and eosinophil infiltration *in vivo* in a guinea pig model of allergic rhinitis.

Conversion of ciclesonide to RM1 by human nasal epithelial cells and animal nasal mucosal homogenates was shown in experiments conducted *in vitro*. This reaction was chiefly mediated by carboxylesterases. Systemic absorption of ciclesonide following intranasal administration was very limited in humans and laboratory animal species (rats and dogs). Comparative clinical studies indicated substantially lower systemic exposure with intranasal compared with inhalational administration.

Repeat dose toxicity studies by the intranasal route were conducted in rats (up to 4 weeks duration) and dogs (up to 6 months) and used higher strengths and/or more frequent administration than is proposed clinically. The nasal spray was well tolerated locally in both species, with no evidence of irritation of the nasal mucosa or other respiratory tract tissues observed at very high multiples of the clinical dose. Atrophy of the mucosal associated lymphoid tissue of the nasal cavity (minimal) and decreased number of goblet cells in the trachea (minimal to slight) were observed in dogs. Major systemic effects comprised suppression of body weight gain and thymic and adrenal cortical atrophy. The local and systemic findings are consistent with corticosteroid activity and substantial dose multiples exist at the NOELs, suggesting limited clinical relevance.

There were no nonclinical objections to the registration of Omnaris nasal spray for the proposed indications.

IV. Clinical Findings

Introduction

The data contained in the submission represent a development program for the new indications of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Although ciclesonide is currently approved for use in asthma the new formulation is not intended to be used for that indication.

Pharmacokinetics

Introduction

The submission contained data from studies that described the pharmacokinetics of ciclesonide following nasal administration. The pharmacokinetics of ciclesonide following oral inhalation have been previously described.

Data submitted in support of pharmacokinetics

Study M1-422 was a randomised, open label, single dose, three period crossover design with washout periods of 7 to 14 days between the treatment periods to compare the systemic des-ciclesonide exposure of Omnaris (ciclesonide) Nasal Spray, ciclesonide hydrofluoroalkane (HFA) nasal aerosol and orally inhaled ciclesonide. The study was conducted at a single centre in the US. The study included male and female subjects in general good health, 18 to 60 years of age, with a body mass index (BMI) between 18 and 28 kg/m^2. The study treatments were:

1. Ciclesonide 300 µg intranasal via aqueous spray
2. Ciclesonide 300 µg intranasal via HFA nasal aerosol
3. Ciclesonide 320 µg orally inhaled via HFA metered dose inhaler (MDI)

Subjects were randomised to study sequence. A total of 30 subjects were randomised and 29 were included in the pharmacokinetic analysis.

Systemic exposure to ciclesonide was lower for the aqueous spray than for HFA nasal spray or orally inhaled ciclesonide. Overall, ciclesonide aqueous spray had low systemic bioavailability.

Study TBN-CL-001 was a single centre, randomised, placebo controlled, double blind, modified sequential study to evaluate the safety, tolerability and pharmacokinetics of multiple doses of ciclesonide nasal spray administered intranasally in healthy volunteers and asymptomatic subjects with SAR. The study was conducted at a single centre in The Netherlands. The study included 48 subjects, age range 18 to 55 years, 34 (71%) subjects were male, and 14 (29%) were female.

Serum concentrations of ciclesonide were below the limit of quantification in the majority of samples and pharmacokinetic parameters were not calculated.

Studies of pharmacokinetic drug interactions with inhaled ciclesonide

Study CP-029 was an open, randomised, three period crossover study in 24 healthy volunteers investigating the pharmacokinetic interactions between inhaled formoterol and inhaled ciclesonide. The study was conducted at a single centre in Germany. The study included 24 subjects: 18 males and six females with an age range of 23 to 45 years, of normal weight and in good general health. The study treatments were:

1. Ciclesonide 800 µg
2. Formoterol 24 µg
3. Ciclesonide 800 µg plus formoterol 24 µg

The treatments were administered as a single dose by oral inhalation. There was a washout period of 7 to 14 days between treatments.

There was a fall in systemic exposure to ciclesonide when administered in combination with formoterol but the decrease was not statistically significant and is unlikely to be clinically significant. There was no effect of ciclesonide upon systemic exposure to formoterol.

Study CP-036 was an open, nonrandomised, one sequence, two period, repeated dose study of the steady state pharmacokinetics of orally inhaled ciclesonide and active metabolite with and without CYP3A4 enzyme inhibition by concomitantly administered ketoconazole. The study was conducted at a single centre in Germany. The study included 14 subjects: ten male, four female, with an age range of 23 to 45 years. The subjects were of normal body weight and in good general health. The study treatments were:

Period 1: inhaled ciclesonide 320 µg once daily for 7 days

Period 2: inhaled ciclesonide 320 µg once daily with orally administered ketoconazole 400 mg once daily for the subsequent 7 days.

There was increased metabolite RM1 exposure of approximately 3.5 fold with concomitant ketoconazole administration. There was no change in parent ciclesonide exposure.

Population pharmacokinetic studies of ciclesonide

Study DMPK US/01-085 was a population pharmacokinetic and pharmacodynamic (PK/PD) analysis of RM1 (metabolite of ciclesonide) and its effect on serum cortisol concentrations using Phase I data. The study examined orally inhaled ciclesonide in the dose range 400 to 3600 µg. The study included data from 14 studies, including 151 subjects: 119 (78.8%) male, 32 (21.1%) female, 12 (7.9%) aged 65 years or more. The RM1 metabolite volume of distribution was affected by weight. There did not appear to be an effect for ciclesonide dose upon cortisol AUC.

Evaluator's overall conclusions on pharmacokinetics

Ciclesonide has very low bioavailability following intranasal administration. Systemic exposure at the 200 µg/day dose level is minimal. Although there are interactions

between formoterol and ketoconazole and ciclesonide these interactions are unlikely to be clinically significant. Ciclesonide does not appear to have an effect upon cortisol AUC.

Pharmacodynamics

Introduction

A single study was submitted that investigated the pharmacodynamic effect of ciclesonide upon endogenous cortisol concentrations.

Data submitted in support of pharmacodynamics

Study FHP012 was an open, two period crossover pilot study on the pharmacodynamics of R-ciclesonide compared to baseline and to budesonide following repeated dose inhalations in 12 healthy male volunteers. The study was conducted at one centre in Germany. The study included 12 healthy male subjects. The study treatments were:

Treatment A: placebo twice daily for two days

Treatment B: 800 µg ciclesonide twice daily for 7 days

Treatment C: 800 µg budesonide twice daily for 7 days

The treatments were administered by oral inhalation. The point estimate (90% confidence interval [CI]) for the ratio of baseline adjusted cortisol ciclesonide/budesonide was 0.68 (0.47 to 0.98). This indicated that µg for µg, ciclesonide had less suppressive effect of cortisol than budesonide. However, there was no difference between the two treatments on adrenocorticotropic hormone (ACTH) stimulation of cortisol: point estimate (90% CI) 1.06 (0.99 to 1.15).

Evaluator's overall conclusions on pharmacodynamics

When administered by oral inhalation, at the same dose level of 800 µg twice daily, ciclesonide had less effect on endogenous cortisol secretion than budesonide.

Efficacy

Introduction

The data presented in support of efficacy represented a development program for the indications of PAR and SAR. This included dose ranging studies and studies in the paediatric population. The studies were conducted in comparison with placebo and there were no comparator controlled studies.

Dose ranging studies

Study TBN-CL-002

Study TBN-CL-002 was a multicentre, double blind, randomised, placebo controlled, parallel group, dose ranging study to assess the safety and efficacy of ciclesonide in adult patients with seasonal rhinitis. The study was conducted at six centres in Texas, US.

The inclusion criteria included:

- Male or female subjects, between 18 and 65 years of age, inclusive
- Good general health and free of any disease or concomitant treatment that could be exacerbated by participation in study, interfere with study conduct, or interfere with the interpretation of the study results as determined by the investigator
- At least a two year history of SAR as assessed by a physician, and currently experiencing nasal allergy symptoms with a minimum score of 8 from a maximum of 12

on the reflective total nasal symptom score (TNSS) (see below) (AM or PM assessment) for at least 3 days during screening

- Demonstrated sensitivity by positive skin testing (by prick or intradermal methods) or by adequately validated *in vitro* tests for specific immunoglobulin E (IgE) (for example, radioallergosorbent test, paper radioimmunosorbent test) to an appropriate seasonal allergen within the past 12 months. A positive skin test was defined as a wheal diameter of at least 3 mm larger than the control for the skin prick test or at least 5 mm larger than the control for the intradermal test. Positive *in vitro* tests were determined by the standards of the individual reference laboratory.

The treatment groups were:

1. 25 mg/day (12.5 µg, one spray each nostril in the morning
2. 50 mg/day (25 µg, one spray each nostril in the morning)
3. 100 mg/day (50 µg, one spray each nostril in the morning)
4. 200 mg/day (100 µg, one spray each nostril in the morning)
5. Placebo

Chlorpheniramine maleate 4 mg every 4 hours (up to 6 doses per day) was used as rescue medication. There was a 7 day screening period, followed by a 14 day treatment period.

The primary efficacy outcome measure was the change from baseline in the summed daily morning (AM) and evening (PM) reflective TNSS over 14 days. The TNSS was a patient rated score defined as the sum of the scores for four nasal symptoms consisting of runny nose, itchy nose, sneezing and nasal congestion. The four nasal symptoms were assessed twice daily from Day –7 (entry into screening period) to Day 14 during the study. Each was rated on a severity scale ranging from 0 to 3. The rating system was as follows:

0 absent (no sign/symptom evident)

1 mild (sign/symptom clearly present, but minimal awareness; easily tolerated)

2 moderate (definite awareness of sign/symptom that is bothersome but tolerable)

3 severe (sign/symptom that is hard to tolerate, causes interference with activities of daily living and/or sleeping, for reflective scores)

The use of reflective TNSS and instantaneous TNSS is recommended in the FDA guidance for development of drugs for allergic rhinitis. The description of the score in the FDA guidance is similar to that used in the TNSS in the present drug development program.

Secondary efficacy endpoints were:

- Patients's global evaluation and Investigator's global evaluation, performed separately but both using the score:
  - Complete relief (virtually no symptoms are present)
  - Marked relief (symptoms are greatly improved and although present, are scarcely troublesome)
  - Moderate relief (symptoms are present and may be troublesome but are noticeably improved)
  - Slight relief (symptoms are present and only minimal improvement has been obtained)
  - Treatment failure (no relief; symptoms are unchanged or worse than pretreatment baseline)
- Instantaneous TNSS

- AUC of reflective TNSS
- Individual reflective symptom scores
- Rescue medication use

Hypothesis testing for the primary and secondary efficacy outcome measures used repeated measures analysis of variance (ANOVA) models. No adjustments were made for multiplicity. The sample size calculation used data from previous studies to estimate effect size and variance. Assuming a two-tailed 0.05 level of significance, 80% power and an average difference between active and placebo of 1.8 units in the summed AM and PM TNSS score (0.9 on the average scale) with a standard deviation of 5.0 (2.5 on the average scale), a sample size of 125 patients per treatment group was required, resulting in a total of 625 patients. To allow for an anticipated dropout rate of 10%, at least 690 patients were to be randomized into the study.

A total of 726 subjects were randomised and 703 (96.8%) completed the study. The treatment groups were similar in demographic and baseline characteristics. The age range was 16.2 to 65.4 years, 512 (70.5%) subjects were female and 214 (29.5%) were male.

There was a significant improvement in TNSS scores for both the 100 mg/day and 200 mg/day doses (Table 2). There was no obvious plateau in effect. There were similar results for reflective TNSS scores, AUC of TNSS scores and instantaneous TNSS scores. There were significant improvements in Patient's global scores for both 100 mg/day and 200 mg/day at Day 7 but only for 200 mg/day at Day 14. There were significant improvements in Investigator's global scores for both 100 mg/day and 200 mg/day at Day 7 but not for either dose at Day 14. For the 200 mg/day dose effects were apparent from Day 3 of treatment. There were no significant differences between the groups in use of rescue medication.

Table 2: Sum of the AM and PM reflective TNSS over two weeks – "intent to treat" (ITT) population

			Difference from Placebo		
Treatment Group	**N[1]**	**LS mean (SD)**	**Estimate**	**95% Confidence Interval**	**p-value[2]**
Baseline sum of the AM and PM reflective TNSS					
A) TBN-15 200 µg	144	18.82 (3.273)			
B) TBN-15 100 µg	145	18.71 (3.369)			
C) TBN-15 50 µg	143	18.35 (3.606)			
D) TBN-15 25 µg	146	18.72 (3.470)			
E) placebo	148	17.80 (3.421)			
Change from baseline in the sum of the AM and PM reflective TNSS over 2 weeks					
A) TBN-15 200 µg	144	-5.83 (4.652)	-1.6421	-2.7357, -0.5484	0.0033
B) TBN-15 100 µg	145	-5.33 (5.092)	-1.1452	-2.2370, -0.0534	0.0398
C) TBN-15 50 µg	142	-4.79 (4.891)	-0.6002	-1.6977, 0.4974	0.2838
D) TBN-15 25 µg	145	-4.81 (4.376)	-0.6211	-1.7129, 0.4706	0.2648
E) placebo	146	-4.19 (4.713)			

[1]Total number of patients with available data. Four patients did not provide adequate post-baseline data and could not be included in the analysis.
[2] For change from baseline treatment comparison, p-value is from mixed-effect ANOVA model with treatment, day and their interaction as fixed effects and patient as a random effect using a compound symmetry correlation structure.
Note: the LS mean (least squares mean) is obtained from ANOVA model.

Study M1-403

Study M1-403 was a randomized, double blind, placebo controlled, parallel group, Phase III clinical trial designed to assess the efficacy and safety of ciclesonide applied as a nasal spray at three dose levels (200 mg, 100 mg or 25 mg once daily) in the treatment of PAR in patients 6-11 years of age. The study was conducted at 74 centres: 59 in the USA and 15 in Canada.

The inclusion criteria included:

- Male or female between the ages of 6 and 11 years, inclusive
- General good health
- History of PAR to a relevant perennial allergen for a minimum of 6 months immediately preceding the study Screening Visit. The PAR must have been of sufficient severity to have required treatment in the past and in the investigators judgment was expected to continue to require treatment for the entire study period.
- A demonstrated sensitivity to at least one allergen known to induce PAR through a standard prick test.

The exclusion criteria included:

- History or physical findings of nasal pathology, including nasal polyps (within the last 60 days) or other clinically significant respiratory tract malformations, recent nasal biopsy (within the last 60 days), nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa (within the last 60 days)
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, the common cold, acute or chronic sinusitis, flu, severe acute respiratory syndrome) within the 14 days preceding screening

- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of b-agonists; intermittent use of b-agonists was acceptable
- Use of antibiotic therapy for acute conditions within 14 days prior to the Screening
- Initiation of immunotherapy during the study period or dose escalation during the study period
- Exposure to systemic corticosteroids for any indication, chronic or intermittent (for example, contact dermatitis), during the past 2 months
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatological conditions during the past 1 month
- Intraocular pressure at screening of 21 mmHg or greater or unsuccessful intraocular pressure (IOP) measurement by the time of the randomization visit
- Glaucoma requiring treatment

The study treatments were:

1. Ciclesonide 100 mg in each nostril once daily
2. Ciclesonide 50 mg in each nostril once daily
3. Ciclesonide 12.5 mg in each nostril once daily
4. Placebo

The study had three phases: baseline 7-14 days, treatment 12 weeks and follow up 7 days.

The primary efficacy outcome variable was the average of AM and PM caregiver/patient reported reflective TNSS over the first 6 weeks of treatment. The secondary efficacy outcome variables were:

- Average of AM and PM caregiver/patient reported reflective TNSS over the 12 weeks of treatment
- The Overall Physician Assessment of Nasal Symptom Severity (PANS) at endpoint
- Average AM and PM caregiver/patient reported reflective TNSS Weeks 7-12 and by each week as well as individual symptom questions over Weeks 1-6, 7-12, 1-12, and each week
- AM caregiver/patient reported reflective TNSS and PM caregiver/patient reported reflective TNSS Weeks 1-6, 7-12, 1-12 and by each week
- Overall reflective average AM and PM caregiver/patient reported TNSS over Weeks 1-6 and 1-12;
- Average AM and PM caregiver/patient reported instantaneous TNSS, AM caregiver/ patient reported instantaneous TNSS, PM caregiver/patient reported instantaneous TNSS and individual symptom questions for average AM and PM instantaneous TNSS Weeks 1-6, 7-12, 1-12, and by each week
- Average AM and PM caregiver/patient reported reflective TNSS by each day over the 12 weeks
- Time to maximal effect
- Onset of action

- Percent change in AM and PM caregiver/patient reported reflective TNSS: Weeks 1-6, 7-12, 1-12, and by each week;
- Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) scores at 3 weeks (T3), 6 weeks (T6), 9 weeks (T9), 12 weeks (T12), and endpoint; average of overall sign and overall symptom scores at T3, T6, T9, and T12 and overall sign score at endpoint; individual sign and individual symptom scores at T3, T6, T9, T12, and endpoint;
- Rescue medication usage.

Safety outcome variables were: adverse events (AEs), vital signs, physical examination, intraocular pressure (IOP) measurements, urinary and plasma cortisol assessment, and routine clinical laboratory tests. During the treatment period there were study visits every 3 weeks.

Hypothesis tests were performed using a repeated measures analysis of covariance (ANCOVA) model. Multiplicity was addressed by using a sequential hypothesis testing procedure. The sample size calculation assumed a standard deviation (SD) for the mean change in TNSS from baseline over 6 weeks to be 1.9. Using this SD, 159 patients per group provided 80% power to detect a difference between treatment groups of 0.6 with a two-sided alpha level of 0.05.

A total of 665 subjects were randomised; 165 to the intranasal ciclesonide 200 mg group, 166 to 100 mg, 169 to 25 mg, and 165 to placebo. Of the randomized subjects 586 (88.1%) completed the study. The age range was 5 to 11 years, 393 (59.2%) subjects were male and 271 (40.8%) were female. Demographic and baseline characteristics were similar for the four treatment groups.

For the primary efficacy outcome variable, there was no significant difference between any of the treatment groups and placebo (Table 3). However, there did appear to be a treatment effect with increasing dose. There was no significant difference between treatment groups in reflective TNSS. Time to maximal effect was 84 days for the 200 mg group. Time to onset of effect was 8 days for the 200 mg group. There was no significant difference between treatment groups in instantaneous TNSS. There was a significant difference for the 200 mg dose in PANS. There was no difference between groups in rescue medication use. Serum concentrations of ciclesonide were below the lowest level of quantification (LLOQ) for the majority of samples.

Table 3: Overview of patients' responses for primary and key secondary efficacy variables – ITT analysis

	Ciclesonide			
	200 mcg	100 mcg	25 mcg	Placebo
Average AM and PM Reflective TNSS				
Baseline				
N	163	164	162	162
Mean (SD)	6.6 (2.22)	6.7 (2.14)	6.8 (2.20)	6.9 (2.31)
Change from Baseline for Weeks 1-6				
N	163	164	162	162
LS mean (SE)	–2.1 (0.16)	–1.8 (0.16)	–1.7 (0.16)	–1.8 (0.16)
Treatment difference vs Placebo	0.312	–0.023	–0.090	
(95% CI)	(–0.1, 0.8)	(–0.5, 0.4)	(–0.5, 0.3)	
p- value[1]	0.164	0.917	0.687	
Average AM and PM Reflective TNSS				
Baseline				
N	163	164	162	162
Mean (SD)	6.6 (2.22)	6.7 (2.14)	6.8 (2.20)	6.9 (2.31)
Change from Baseline for Weeks 1-12				
N	163	164	162	162
LS mean (SE)	–2.3 (0.16)	–2.0 (0.16)	–1.9 (0.16)	–2.2 (0.16)
Treatment difference vs Placebo	0.146	–0.137	–0.238	
(95% CI)	(–0.3, 0.6)	(–0.6, 0.3)	(–0.7, 0.2)	
p-value[1]	0.528	0.553	0.304	
Physician Assessment of Nasal Symptom Severity				
Baseline				
N	157	163	164	155
Mean (SD)	7.3 (2.66)	7.2 (2.78)	7.0 (2.69)	6.7 (2.91)
Change from Baseline to Endpoint				
N	157	163	164	155
LS mean (SE)	-2.8 (0.21)	-2.0 (0.21)	-2.2 (0.20)	–2.0 (0.21)
Treatment difference vs Placebo	0.796	-0.001	0.223	
(95% CI)	(0.2, 1.4)	(-0.6, 0.6)	(-0.3, 0.8)	
p-value[2]	0.006	0.998	0.429	

[1] P-value is from a repeated measures ANCOVA with treatment, baseline, week, and treatment-by-week interaction; Week is treated as an unordered categorical variable. A first order AR(1) structure was used to model intra-patient correlation, in combination with treating patient as a random effect. Baseline is the average of AM and PM TNSS over the baseline period (up to seven days prior to randomization).

[2] P-value is from an ANCOVA with pooled center, treatment, and baseline. Baseline is the measurement at the T0 Visit. Endpoint refers to the patient's last measurement.

Studies conducted in environmental exposure chambers

Study M1-406

Study M1-406 was a randomised, double blind, placebo controlled, single centre, parallel group study conducted in an Environmental Exposure Chamber (EEC). An EEC is stated to be "a validated outpatient clinical research facility designed to allow controlled exposure to airborne pollen particles with consistent airborne pollen particle counts between 3000 to 4000 pollen grains/m^3, documented by conducting assessments every thirty minutes using seven Rotational Impaction Samplers". The study was conducted at a single centre in Canada.

The inclusion criteria included:

- Male or female patients 18 years and older
- General good health

- History of SAR to short ragweed pollen for a minimum of two years immediately preceding the study entry. In the investigator's judgment, the SAR during this two year period must have been of sufficient severity and would be expected to require treatment during the ragweed season.
- A demonstrated sensitivity to short ragweed pollen known to induce SAR through a standard skin prick test.

The treatment groups were:

1. Ciclesonide 50 mg per actuation, two actuations in each nostril, self administered
2. Placebo

The treatments were administered once. Subjects were randomised and blinded.

The primary efficacy outcome measure was the time to onset of action, measured by a difference between the ciclesonide and the placebo groups in the change from baseline in patient assessed instantaneous TNSS following treatment. Secondary efficacy outcome measures were:

- Change in TNSS from baseline at each time point
- Changes in individual nasal symptom scores from baseline at each time point
- The proportion of patients exhibiting good/excellent response at each time point defined as all components of the patient assessed TNSS scored as mild or less in severity.

A total of 503 subjects were randomised, 251 to ciclesonide and 252 to placebo. One subject in the placebo group did not receive treatment. All 251 treated subjects in each treatment group were included in the "intent to treat" (ITT) analysis. No subject discontinued prematurely. The age range was 18 to 75 years, 274 (54.6%) subjects were female and 228 (45.4%) were male.

There was a statistically significant difference in response between ciclesonide and placebo from one hour post dosing, with maximum effect size at that time point (Table 4). A higher proportion of subjects in the ciclesonide group reported good or excellent response. Nasal stuffiness was less in the ciclesonide group at one hour: treatment difference (95% CI) 0.2 (0.04 to 0.28) p=0.006. Nasal itching was less in the ciclesonide group at one hour: treatment difference (95% CI) 0.1 (0.00 to 0.26) p=0.026. There was no difference between treatment groups in sneezing. Rhinorrhoea was less in the ciclesonide group at one hour: treatment difference (95% CI) 0.1 (0.00 to 0.25) p=0.025.

Table 4: Instantaneous TNSS: 0 to 12 hours - ITT

	Treatment	
	Ciclesonide 200 mcg (N=251)	Placebo (N=251)
Baseline (Hour 0)		
N	251	251
Mean (SD)	9.9 (1.90)	9.9 (1.86)
Change from Baseline for Hour 1		
N	251	251
LS mean (SE)	-2.3 (0.15)	-1.8 (0.15)
Treatment difference (95% CI); p-value[1]	0.5 (0.08, 0.93); p=0.010	
Change from Baseline for Hour 2		
N	251	251
LS mean (SE)	-2.1 (0.16)	-1.6 (0.16)
Treatment difference (95% CI); p-value[1]	0.5 (0.03, 0.90); p=0.018	
Change from Baseline for Hour 3		
N	251	251
LS mean (SE)	-2.0 (0.17)	-1.5 (0.17)
Treatment difference (95% CI); p-value[1]	0.5 (0.07, 1.00); p=0.012	
Change from Baseline for Hour 4		
N	251	251
LS mean (SE)	-2.0 (0.16)	-1.3 (0.16)
Treatment difference (95% CI); p-value[1]	0.7 (0.21, 1.10); p=0.002	
Change from Baseline for Hour 5		
N	251	251
LS mean (SE)	-1.8 (0.16)	-1.2 (0.16)
Treatment difference (95% CI); p-value[1]	0.6 (0.11, 1.02); p=0.008	
Change from Baseline for Hour 6		
N	251	251
LS mean (SE)	-1.8 (0.16)	-1.0 (0.16)
Treatment difference (95% CI); p-value[1]	0.7 (0.27, 1.18); p<0.001	
Change from Baseline for Hour 7		
N	251	251
LS mean (SE)	-1.6 (0.16)	-1.1 (0.16)
Treatment difference (95% CI); p-value[1]	0.5 (0.06, 0.97); p=0.014	
Change from Baseline for Hour 8		
N	251	251
LS mean (SE)	-1.6 (0.16)	-0.9 (0.16)
Treatment difference (95% CI); p-value[1]	0.7 (0.23, 1.13); p=0.001	
Change from Baseline for Hour 9		
N	251	251
LS mean (SE)	-1.5 (0.16)	-0.7 (0.16)
Treatment difference (95% CI); p-value[1]	0.8 (0.35, 1.22); p<0.001	
Change from Baseline for Hour 10		
N	251	251
LS mean (SE)	-1.6 (0.16)	-0.7 (0.16)
Treatment difference (95% CI); p-value[1]	0.9 (0.46, 1.36); p<0.001	
Change from Baseline for Hour 11		
N	251	250
LS mean (SE)	-1.3 (0.16)	-0.5 (0.16)
Treatment difference (95% CI); p-value[1]	0.8 (0.38, 1.28); p<0.001	
Change from Baseline for Hour 12		
N	251	251
LS mean (SE)	-1.4 (0.17)	-0.5 (0.17)
Treatment difference (95% CI); p-value[1]	0.9 (0.41, 1.34); p<0.001	

[1] one-sided p-value value was from an ANCOVA with treatment and baseline as covariates.

Study M1-407

Study M1-407 was a randomised, double blind, placebo controlled, single centre, parallel group study conducted in an Environmental Exposure Unit (EEU) to determine the time to onset of action of ciclesonide, applied as a nasal spray (200 mg once daily) in patients with SAR. The study was of similar design to M1-406 and was conducted at a single centre in Canada.

The inclusion criteria included:

- Male or female patients aged 18 years and older
- In general good health
- History of SAR to short ragweed pollen for a minimum of two years immediately preceding the study entry. In the investigator's judgment, the SAR during this two year period must have been of sufficient severity and would be expected to require treatment during the ragweed season
- A demonstrated sensitivity to short ragweed pollen known to induce SAR through a standard skin prick test

The treatment groups were:

1. Ciclesonide 50 mg per actuation, two actuations in each nostril, self administered
2. Placebo

The treatments were administered once. Subjects were randomised and blinded.

The primary efficacy outcome measure was the time to onset of action, measured by a difference between the ciclesonide and the placebo groups in the change from baseline in patient-assessed instantaneous TNSS following treatment. Secondary efficacy outcome measures were:

- Change in TNSS from baseline at each time point
- Changes in individual nasal symptom scores from baseline at each time point
- The proportion of patients exhibiting good/excellent response at each time point defined as all components of the patient-assessed TNSS scored as mild or less in severity.

A total of 420 subjects were randomised, 210 to each treatment group, all subjects were included in the ITT analysis and 208 (99%) in the ciclesonide group and 209 (99.5%) in the placebo group completed the study. The age range was 18 to 71 years, 242 (57.6%) were female and 178 (42.4%) were male.

There was a statistically significant improvement in instantaneous TNSS at Hour 6: treatment difference (95% CI) 0.7 (0.06 to 1.32), p=0.016; and also at Hour 7: 0.6 (-0.00, 1.27); p=0.025. However there was no significant difference between treatments at the other time points. A higher proportion of subjects in the ciclesonide group reported good or excellent response from Hour 6 to Hour 12 (with the exception of Hour 10) (Table 5). There was less nasal stuffiness/congestion at Hours 8 and 12 in the ciclesonide group. There was no significant difference between treatment groups for nasal itching, sneezing or runny nose/rhinorrhoea.

Table 5: Hourly assessment of patient reported Good/Excellent response

Hour	% Good/Excellent Response		Odds Ratio	95% CI for Odds Ratio	p-value[(1)]
	Ciclesonide	Placebo			
-1.5	9.5%	10.5%	0.9	0.5, 1.7	0.3311
-1.0	0.5%	1.0%	0.5	0.0, 5.4	0.2759
-0.5	0	0			
0	0	0			
1	15.7%	11.0%	1.5	0.8, 2.6	0.0913
2	25.2%	22.9%	1.1	0.7, 1.8	0.3223
3	35.7%	26.7%	1.5	1.0, 2.3	0.0267
4	30.5%	24.8%	1.3	0.8, 2.0	0.1100
5	26.2%	22.0%	1.2	0.8, 2.0	0.1865
6	31.0%	21.5%	1.6	1.0, 2.5	0.0173
7	30.6%	22.5%	1.5	1.0, 2.3	0.0361
8	27.8%	17.7%	1.8	1.1, 2.8	0.0085
9	26.3%	16.7%	1.8	1.1, 2.8	0.0108
10	25.4%	18.7%	1.5	0.9, 2.3	0.0592
11	24.0%	16.7%	1.6	1.0, 2.5	0.0380
12	25.5%	16.7%	1.7	1.0, 2.7	0.0180

[(1)] one-sided p-value for logistical regression with adjustment for treatment and baseline TNSS

Study M1-413

Study M1-413 was a randomised, double blind, placebo controlled, single centre, parallel group study conducted in an EEC to determine the time to onset of action of ciclesonide, applied as a nasal spray (200 µg once daily) in patients with SAR. The study was conducted at a single centre in Canada.

The study was identical in design to Studies M1-406 and M1-407.

A total of 509 subjects were randomised to treatment: 255 to ciclesonide, 254 to placebo. All subjects were included in the ITT population. Of the randomised subjects 255 (100%) in the ciclesonide group and 253 (99.6%) in the placebo group completed the study. The age range was 18 to 69 years, 279 (54.8%) subjects were female and 230 (45.2%) were male.

There was a significant improvement in instantaneous TNSS score in the ciclesonide group relative to placebo at Hour 6: treatment difference (95% CI) 0.53 (0.03 to 1.03) p=0.018; and also at Hours 7, 9, 10 and 11 (Table 6). There was no significant difference between the treatment groups in the proportion of subjects reporting good or excellent response at any time point. Nasal stuffiness/congestion was improved in the ciclesonide group at Hour 12: treatment difference (95% CI) 0.17 (0.04 to 0.30) p=0.006. There was no significant difference between the groups in nasal itching. Sneezing was improved in the ciclesonide group at Hour 12: treatment difference (95% CI) 0.20 (0.04 to 0.36) p=0.007. There was a significant improvement in rhinorrhoea in the ciclesonide group at Hour 10: treatment difference (95% CI) 0.15 (0.02 to 0.29) p=0.015.

Table 6: Instantaneous TNSS: 0 to 12 hours –ITT

	Treatment	
	Ciclesonide 200 mcg (N=255)	Placebo (N=254)
Baseline (Hour 0)		
N	255	254
Mean (SD)	10.17 (1.68)	10.07 (1.72)
Change from Baseline for Hour 1		
N	255	254
LS mean (SE) change	-2.19 (0.15)	-2.42 (0.15)
Treatment difference (95% CI); p-value[1]	-0.22 (-0.65, 0.20); p=0.850	
Change from Baseline for Hour 2		
N	255	254
LS mean (SE) change	-2.45 (0.16)	-2.63 (0.17)
Treatment difference (95% CI); p-value[1]	-0.18 (-0.64, 0.28); p=0.778	
Change from Baseline for Hour 3		
N	255	254
LS mean (SE) change	-2.67 (0.17)	-2.70 (0.17)
Treatment difference (95% CI); p-value[1]	-0.03 (-0.51, 0.44); p=0.556	
Change from Baseline for Hour 4		
N	255	254
LS mean (SE) change	-2.68 (0.17)	-2.36 (0.17)
Treatment difference (95% CI); p-value[1]	0.32 (-0.16, 0.80); p=0.094	
Change from Baseline for Hour 5		
N	255	253
LS mean (SE) change	-2.44 (0.18)	-2.26 (0.18)
Treatment difference (95% CI); p-value[1]	0.17 (-0.32, 0.66); p=0.249	
Change from Baseline for Hour 6		
N	255	253
LS mean (SE) change	-2.53 (0.18)	-2.00 (0.18)
Treatment difference (95% CI); p-value[1]	0.53 (0.03, 1.03); p=0.018	
Change from Baseline for Hour 7		
N	255	253
LS mean (SE) change	-2.32 (0.17)	-1.87 (0.18)
Treatment difference (95% CI); p-value[1]	0.45 (-0.04, 0.93); p=0.036	
Change from Baseline for Hour 8		
N	255	253
LS mean (SE) change	-2.03 (0.17)	-1.79 (0.17)
Treatment difference (95% CI); p-value[1]	0.25 (-0.22, 0.71); p=0.151	
Change from Baseline for Hour 9		
N	255	253
LS mean (SE) change	-2.12 (0.17)	-1.72 (0.17)
Treatment difference (95% CI); p-value[1]	0.40 (-0.07, 0.87); p=0.048	
Change from Baseline for Hour 10		
N	255	253
LS mean (SE) change	-2.00 (0.17)	-1.45 (0.17)
Treatment difference (95% CI); p-value[1]	0.55 (0.08, 1.03); p=0.011	
Change from Baseline for Hour 11		
N	255	253
LS mean (SE) change	-2.03 (0.17)	-1.57 (0.17)
Treatment difference (95% CI); p-value[1]	0.46 (-0.03, 0.94); p=0.032	
Change from Baseline for Hour 12		
N	255	253
LS mean (SE) change	-1.95 (0.17)	-1.35 (0.17)
Treatment difference (95% CI); p-value[1]	0.60 (0.11, 1.08); p=0.008	

[1] one-sided p-value value was from an ANCOVA with treatment and baseline as covariates.

Pivotal efficacy studies

Study M1-401

Study M1-401 was a multicentre, randomised, double blind, parallel group, placebo controlled clinical trial to assess the efficacy, safety and effect on quality of life of once daily, intranasal ciclesonide 200 µg in adult and adolescent patients with SAR. The study was conducted at six centres in the US.

The inclusion criteria included:

- Males or females 12 years and older
- General good health and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results or put the patient at increased risk during the trial
- History of SAR to the relevant seasonal allergen for a minimum of two years immediately preceding the study season. The SAR must have been of sufficient severity to have required treatment (continuous or intermittent) in the past and in the investigator's judgment was expected to require treatment throughout the entire study period
- A demonstrated sensitivity to mountain cedar pollen known to induce SAR through a standard prick test. A positive test was defined as a wheal diameter at least three millimeters larger than the control wheal for the prick test. Documentation of a positive result 12 months prior to screening was acceptable.
- Female was of child bearing potential and was currently taking and would continue to use a medically reliable method of contraception for the entire study duration
- Women of childbearing potential or less than one year postmenopausal required a negative serum pregnancy test at the screening visit as well as at last on-treatment visit

The exclusion criteria included:

- Pregnancy, nursing, or plans to become pregnant or donate gametes (ova or sperm) for *in vitro* fertilization during the study period or for 30 days following the study period
- History or physical findings of nasal pathology, including nasal polyps (within the last 60 days) or other clinically significant respiratory tract malformations, recent nasal biopsy
- A known hypersensitivity to any corticosteroid
- History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, the common cold, acute or chronic sinusitis, flu, severe acute respiratory syndrome) within the 14 days preceding the screening visit or development of a respiratory infection during the baseline period
- History of alcohol or drug abuse within the preceding two years
- History of a positive test for HIV, hepatitis B or hepatitis C
- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of b-agonists; intermittent use of b-agonists was acceptable

- Plans to travel outside the study area (the known pollen area for the investigative site) for two or more consecutive days or five or more days total during the five week study period (Baseline and Treatment Periods)
- Use of any prohibited concomitant medications within the prescribed (per protocol) time spent last dose period prior to the screening visit and during entire treatment duration
- Use of antibiotic therapy for acute conditions within 14 days prior to the screening visit. Low doses of antibiotics taken for prophylaxis were permitted if the therapy was started prior to the screening visit and was expected to continue throughout the trial
- Initiation of immunotherapy during the study period or dose escalation during the study period
- Previous participation in an intranasal ciclesonide study
- Non-vaccinated exposure to or active infection with, chickenpox or measles within the 21 days preceding the trial
- Exposure to systemic corticosteroids for any indication, chronic or intermittent (for example, contact dermatitis) during the past two months or presence of an underlying condition that could reasonably be expected to require treatment with corticosteroids during the course of the study
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatological conditions during the past one month, or presence of an underlying condition that could reasonably be expected to require treatment with such preparations during the course of the study

The treatment groups were:

1. Ciclesonide 50 mg per actuation, 2 sprays in each nostril in the morning
2. Placebo

Subjects were blinded to treatment and block randomised. Prohibited medicines included steroids, vasoconstrictors, antihistamines, cough and cold preparations, major tranquilisers, antiepileptics, tricyclics antidepressants and other immunoactive drugs. There was a baseline period of 7 to 10 days, a treatment period of 4 weeks and a follow up period of 7 days.

The primary efficacy outcome measure was the average of AM and PM patient assessed reflective TNSS over the first two weeks of treatment. The secondary efficacy outcome measures were:

- Average of AM and PM patient assessed instantaneous TNSS over the first two weeks of treatment
- PANS at endpoint
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at endpoint
- Total non-nasal symptoms (reflective)
- Individual symptoms for nasal and non-nasal symptoms
- Time to onset of effect
- Time to maximal effect

- Percent change in AM and PM reflective TNSS at selected time points (first two weeks of treatment, second two weeks of treatment, overall four weeks and each day)
- Average and separate AM and PM reflective TNSS, respectively, at selected time points (second two weeks of treatment, overall four weeks and each day)
- Average and separate AM and PM instantaneous TNSS, respectively, at selected time points (second two weeks of treatment, overall four weeks, and each day)
- Individual components of the PANS and PANS at selected time points (first two weeks of treatment, second two weeks of treatment, overall four weeks)
- RQLQ score for changes from baseline at two weeks and four weeks for overall
- RQLQ score as well as for each of the seven domains for the adult RQLQ and the six domains for the adolescent RQLQ.

Safety outcome measures were: adverse events (AEs), vital signs, physical examination and ear, nose and throat (ENT) findings and routine laboratory tests.

Statistical Considerations

Hypothesis tests were performed using repeated measures analysis of covariance. Onset of action was assessed using a t-test.

The sample size calculation assumed a SD in reflective TNSS of 2.4 and calculated that in order to detect a difference between treatment groups in reflective TNSS of 0.9 with a power of 90%, an alpha of 0.05, and a randomisation ratio of 1:1, 151 subjects would be required in each treatment arm.

Results for Study M1-401

A total of 490 subjects were screened, 327 were randomised and 292 (89.3%) completed. Twenty one (12.8%) subjects in the ciclesonide group and 14 (8.6%) in the placebo group discontinued: nine in the ciclesonide and four in the placebo group because of AEs. The age range was 12 to 86 years, 212 (64.8%) subjects were female and 115 (35.2%) were male. The treatment groups were similar in demographic characteristics and baseline disease characteristics. Concomitant medication use during the treatment period was similar for the two treatment groups.

There was a statistically significant benefit for ciclesonide for the primary efficacy outcome measure: treatment difference (95% CI) 0.90 (0.45 to 1.36) $p<0.001$ (Table 7). This was the magnitude of treatment difference that the study was designed to detect but it is not clear what the clinical significance of this improvement is. The results for some secondary efficacy outcome measures were:

- A statistically significant benefit for ciclesonide in the average of AM and PM patient-assessed instantaneous TNSS over the first two weeks of treatment: treatment difference (95% CI) 0.88 (0.44 to 1.31) $p<0.001$ (Table 7)
- No difference between the treatment groups in PANS at endpoint (Table 7)
- No significant difference between the treatment groups in RQLQ at endpoint (Table 7)
- There was no difference between treatments in total non-nasal symptoms (reflective)

Table 7: Overview of patients' responses for primary and key secondary efficacy variables - ITT analysis

	Treatment	
	Ciclesonide 200 mcg	**Placebo**
Average AM and PM Reflective TNSS		
Baseline		
N	162	162
Mean (SD)	8.96 (1.96)	8.83 (1.82)
Change from Baseline for Days 1-14		
N	162	162
LS mean (SE)	-2.40 (0.16)	-1.50 (0.16)
Treatment difference (95% CI); p-value[1]	0.90 (0.45, 1.36); p<0.001	
Average AM and PM Instantaneous TNSS		
Baseline		
N	163	162
Mean (SD)	8.40 (2.24)	8.33 (2.08)
Change from Baseline for Days 1-14		
N	163	162
LS mean (SE)	-2.15 (0.16)	-1.28 (0.16)
Treatment difference (95% CI); p-value[1]	0.88 (0.44, 1.31); p<0.001	
PANS		
Baseline		
N	163	161
Mean (SD)	7.97 (1.58)	8.07 (1.44)
Change from Baseline to Endpoint		
N	163	161
LS mean (SE)	-1.98 (0.157)	-1.99 (0.158)
Treatment difference (95% CI); p-value[2]	-0.01 (-0.44, 0.43); p=0.982	
Combined Adult and Adolescent RQLQ		
Baseline		
N	151	152
Mean (SD)	3.96 (1.05)	3.78 (0.98)
Change from Baseline to Endpoint		
N	151	152
LS mean (SE)	-1.39 (0.112)	-1.21 (0.111)
Treatment difference (95% CI); p-value[2]	0.18 (-0.13, 0.49); p=0.244	

[1]p-value is from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction; Day is treated as an unordered categorical variable. A first order AR(1) structure was used to model intra-patient correlation and, in combination with treating patient as a random effect, this yielded a correlation structure in which observations from the same patient were considered correlated with observations closer in time being more correlated. Baseline is the average of AM and PM TNSS over the baseline period (up to seven days prior to randomization).
[2]p-value is from an ANCOVA with center, treatment, and baseline. Baseline is the measurement at the T0 Visit. Endpoint refers to the patient's last measurement.

The results for the other secondary efficacy outcome measures were:

- There was a significant difference in reflective TNSS was for both AM and PM time points
- There was a significant difference for all the individual components of reflective TNSS
- There was a statistically significant improvement in instantaneous TNSS in the ciclesonide group compared with placebo throughout the treatment period

- Time to onset of effect, as determined by instantaneous TNSS, was 12 hours
- The largest treatment difference in AM and PM reflective TNSS (maximal effect) was 1.37, which occurred on Day 12 (time to maximal effect)
- There were no differences between the treatment groups in individual components of the PANS from baseline to end point
- The analyses of the separate domains of the adult RQLQ and the adolescent RQLQ were not presented

Study M1-402

Study M1-402 was a multicentre, randomised, double blind, placebo controlled, parallel group study of intranasally administered ciclesonide 200 mg once daily in subjects with PAR. The study was conducted at 41 centres in the US and Canada.

The inclusion criteria included:

- Male or female, 12 years and older.
- General good health and free of any concomitant conditions or treatment that could interfere with study conduct, influence the interpretation of study observations/results or put the patient at increased risk during the trial.
- A history of PAR to a relevant perennial allergen for a minimum of two years immediately preceding the study. The PAR must have been of sufficient severity to have required treatment (continuous or intermittent) in the past and in the Investigator's judgment was expected to require treatment throughout the entire study period.
- A demonstrated sensitivity to at least one allergen known to induce PAR through a standard prick test. A positive test is defined as a wheal diameter at least 3 mm or larger than the control wheal. Additionally, the patient is expected to be exposed to the PAR allergen that he/she has tested positive for via the skin prick test for the duration of the study.
- Female is of childbearing potential and is currently taking and will continue to use a medically reliable method of contraception for the entire study duration
- The exclusion criteria were similar to those for Study M1-401, with the addition of:
- Patients allergic to a seasonal aeroallergen, for example, trees, grasses or weeds, with seasonal exacerbation anticipated to occur, or occurring, during the study.

The treatment groups were:

1. Ciclesonide 50 mg per actuation, 2 sprays in each nostril in the morning
2. Placebo

Subjects were blinded to treatment and block randomised. Prohibited medicines included steroids, vasoconstrictors, antihistamines, cough and cold preparations, major tranquilisers, antiepileptics, tricyclics antidepressants and other immunoactive drugs. There was a baseline period of 7 to 14 days, a treatment period of 6 weeks and a follow up period of at least 7 days.

The primary efficacy outcome measure was the average of AM and PM patient assessed reflective TNSS over Days 1-42. Secondary efficacy outcome measures were:

- Average of AM and PM patient-assessed instantaneous TNSS over Days 1-42
- PANS at endpoint
- Combined Adult and Adolescent RQLQ at endpoint
- Individual symptoms for nasal symptoms at selected time points (Days 1-42, Days 1-14, Days 15-28, Days 29-42 and each day)
- Time to onset of action
- Time to maximal effect
- Percent change in reflective TNSS, at selected time points (Days 1-42, Days 1-14, Days 15-28, Days 29-42 and each day)
- Average and separate AM and PM reflective TNSS, at selected time points (Days 1-42, 1-14, 15-28, 29-42 and each day)
- Average and separate AM and PM instantaneous TNSS, respectively, at selected time points (Days 1-42, 1-14, 15-28, 29-42 and each day)
- Individual components of the PANS at 3 weeks (T3), 6 weeks (T6) and endpoint and overall PANS at T3 and T6
- Overall combined adult and adolescent RQLQ score for changes from baseline at T3 and T6 and for overall adult and adolescent RQLQ scores separately, as well as for each of the seven domains for the adult RQLQ and the six domains for the adolescent RQLQ.

The safety outcome measures were: AEs, vital signs, physical examination, ENT findings, and clinical laboratory tests.

Statistical Considerations

Hypothesis tests were performed using repeated measures analysis of covariance. Onset of action was assessed using a t-test. Multiplicity was not addressed because of the use of "closed testing procedures".

The sample size calculation assumed a SD in reflective TNSS of 2.6, and calculated that in order to detect a difference between treatment groups in reflective TNSS of 0.7 with a power of 90%, an alpha of 0.05, and a randomisation ratio of 1:1, 209 subjects would be required in each treatment arm.

Results for Study M1-402

A total of 676 subjects were screened, 471 subjects were randomised and, of these, 409 (86.8%) completed the study. There were 32 (13.4%) subjects in the ciclesonide group, and 30 (12.9%) in the placebo group who discontinued. The age range was 12 to 75 years, 305 (64.8%) subjects were female and 166 (35.2%) were male. A smaller proportion of subjects in the ciclesonide group used a historical skin prick test on entry: 71 (29.8%) compared with 81 (34.8%) in the placebo group. Apart from this, the treatment groups were similar in demographic characteristics. More subjects in the ciclesonide group used salbutamol during the treatment phase: 28 (11.8%) compared with 14 (6.0%) in the placebo group.

There was a statistically significant improvement in reflective TNSS in the ciclesonide group compared with placebo: treatment difference (95% CI) 0.63 (0.28 to 0.97) $p<0.001$ (Table 8). The treatment difference detected was less than that for which the study was powered. There was also a statistically significant improvement in instantaneous TNSS:

treatment difference (95% CI) 0.54 (0.21 to 0.88) p=0.001 (Table 8). There was no significant difference between the treatment groups in PANS (Table 8). There was a statistically significant decrease in RQLQ in the ciclesonide group relative to placebo: treatment difference (95% CI) 0.28 (0.07 to 0.50) p=0.011 (Table 8).

Table 8: Overview of patients' responses for primary and key secondary efficacy variables - ITT analysis

	Treatment	
	Ciclesonide 200 mcg	**Placebo**
Average AM and PM Reflective TNSS		
Baseline		
N	232	229
Mean (SD)	7.59 (2.04)	7.72 (2.14)
Change from Baseline for Days 1-42		
N	232	229
LS mean (SE)	-2.51 (0.12)	-1.89 (0.13)
Treatment difference (95% CI); p-value[1]	0.63 (0.28, 0.97); p<0.001	
Average AM and PM Instantaneous TNSS		
Baseline		
N	232	229
Mean (SD)	7.07 (2.15)	7.09 (2.27)
Change from Baseline for Days 1-42		
N	232	229
LS mean (SE)	-2.22 (0.12)	-1.68 (0.12)
Treatment difference (95% CI); p-value[1]	0.54 (0.21, 0.88); p=0.001	
PANS		
Baseline		
N	233	230
Mean (SD)	6.91 (1.98)	6.81 (2.05)
Change to Endpoint		
N	233	230
LS mean (SE)	-2.05 (0.148)	-1.67 (0.148)
Treatment difference (95% CI); p-value[2]	0.38 (0.00, 0.76); p=0.051	
Combined Adult and Adolescent RQLQ		
Baseline		
N	211	202
Mean (SD)	3.32 (1.08)	3.38 (1.10)
Change to Endpoint		
N	211	202
LS mean (SE)	-1.30 (0.084)	-1.01 (0.085)
Treatment difference (95% CI); p-value[2]	0.28 (0.07, 0.50) p=0.011	

[1]p-value is from a repeated measures ANCOVA with treatment, baseline, day, and treatment by day interaction; day is an unordered categorical variable. An AR(1) model in conjunction with treating patient as a random effect was used to model intra-patient correlation. Baseline is the average of AM and PM TNSS over the baseline period (up to 7 days prior to randomization).

[2]p-value is from an ANCOVA with center, treatment, and baseline. Baseline is the measurement at the T0 Visit. Endpoint refers to the patient's last measurement.

The improvement in reflective TNSS occurred during all time intervals during treatment. However, although statistically significant, the percent change in reflective TNSS was disappointing with at best a 10% improvement with ciclesonide. The improvement in reflective TNSS occurred in both the morning and evening. For individual reflective TNSS

symptoms, there were improvements in nasal itching, sneezing and runny nose but not for nasal congestion. Instantaneous TNSS was also improved in the ciclesonide group relative to placebo during all the time periods. Similar to the reflective TNSS findings, for individual instantaneous TNSS symptoms, there were improvements in nasal itching, sneezing and runny nose but not for nasal congestion. The largest treatment difference in AM and PM reflective TNSS was 1.05, which occurred on Day 37 (time to maximal effect). The first time point where there was a significant difference in instantaneous TNSS was at 9 hours post dose (treatment difference (95% CI) 0.45 (0.03 to 0.87) p=0.0343; and this is taken to be the time to onset of effect. For the individual domains of the RQLQ, there were improvements in activities, sleep, non-nose/eye symptoms, practical problems and nasal symptoms, but not for eye symptoms or the emotional domain. There were no significant differences for any of the domains of the adolescent RQLQ.

Additional studies supportive of efficacy

Study M1-404

Study M1-404 was a multicentre, randomised, double blind, placebo controlled, parallel group study to investigate the long term safety of ciclesonide, applied as a nasal spray, once daily in patients with PAR. The study was conducted at 35 centres in the US.

The inclusion criteria included:

- Male or female, aged 12 years and older.
- General good health
- History of PAR for a minimum of two years preceding screening visit, of sufficient severity to require treatment (either continuous or intermittent) in the past and, in the investigator's judgment, expected to continue to require treatment for the study duration.
- Demonstrated sensitivity to at least one allergen known to induce PAR through a standard skin prick or intradermal test
- Positive allergen test must have been consistent with medical history of PAR

The study treatments were:

1. Ciclesonide nasal spray, 50 mg per actuation, 2 actuations in each nostril once daily
2. Placebo

Subjects were randomised and blinded to treatment allocation. There was a baseline period of 7 to 14 days, followed by a treatment period of 52 weeks.

The efficacy outcome measures were:

- Changes from baseline in reflective 24 hour AM TNSS
- Individual patient-assessed nasal symptoms
- Percent change in patient's self assessed reflective 24 hour TNSS
- PANS at endpoint and at other selected time points
- Combined Adult and Adolescent RQLQ at endpoint and at other selected time points
- Resource utilization/health economics information were measured throughout the study

The safety outcome measures were: AEs, physical examination findings, vital signs, ENT examination findings, electrocardiogram (ECG) findings, clinical laboratory tests, urine (24 hour) and AM plasma cortisol (subset of patients randomized at pre-selected sites), and eye examinations (IOP measurements, cataract assessment using LOCS III criteria, visual acuity and overall ocular health).[2]

Sample size was determined by the requirements of the International Council on Harmonisation (ICH) Guidelines that 300 patients should be exposed to ciclesonide nasal spray for six months and 100 patients be exposed for one year. In order to account for withdrawals, 600 patients were to be randomized in a 2:1 ratio (400 ciclesonide: 200 placebo).

The study was not designed primarily as an efficacy study. Hence, although efficacy measures were performed the sample size was not based on power calculations.

A total of 663 subjects were randomised: 441 to ciclesonide, and 222 to placebo. Of the randomised subjects, 318 (72.1%) subjects in the ciclesonide group and 156 (70.3%) in the placebo group completed the study. The age range was 12 to 74 years, 436 (65.8%) subjects were female and 227 (34.2%) were male. The treatment groups were similar in demographic and baseline characteristics.

There was a statistically significant improvement in reflective TNSS for all time periods through to 52 weeks in the ciclesonide group compared with placebo. However this translated to at best a 21.8% improvement in reflective TNSS for ciclesonide compared with placebo. Over the course of the study there were statistically significant improvements with ciclesonide for each of the symptom components of the TNSS. However, there was no difference in PANS. Overall there was a statistically significant improvement in RQLQ, but not at individual time points.

Efficacy data from studies conducted in children

Study M1-416

Study M1-416 was a multicentre, randomised, double blind, placebo controlled, multicenter, parallel group study to evaluate the safety and tolerability of ciclesonide 200 mg administered once daily as an intranasal spray for 12 weeks in paediatric patients (ages 2 to 5 years) with PAR. The study was conducted at three centres in the US.

The inclusion criteria included:

- Male or female between the ages of 2 and 5 years, inclusive
- General good health
- Demonstrated sensitivity to at least one allergen known to induce PAR through a standard skin prick test within one year of study start. A positive test was defined as a wheal diameter at least 3 mm larger than the control wheal for the skin prick test.
- History of PAR for a minimum of 90 days immediately preceding the study Screening Visit, of sufficient severity to require treatment (either continuous or intermittent) during this period and could be expected to continue to require treatment for the study duration

[2] The Lens Opacities Classification System, Version III (LOCS III) is means of subjectively grading the type and severity of age-related cataract (ARC) in vivo by comparing a patient's cataract to a set of standard photographs that illustrate differing degrees of nuclear, cortical, and posterior subcapsular cataract formation.

- The positive allergen test must be consistent with the medical history of PAR. The patient is expected to be exposed to the same allergen during the entire duration of the study.

The exclusion criteria included:

- History or physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma, or surgery and atrophic rhinitis or rhinitis medicamentosa within 60 days of screening
- Hypersensitivity to any corticosteroid or any of the excipients in the study drug formulation
- Respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, the common cold, acute or chronic sinusitis, flu, severe acute respiratory syndrome) within 14 days of screening
- History of a positive test for HIV, hepatitis B or hepatitis C;
- Active asthma requiring treatment with inhaled or systemic corticosteroids and/or routine use of b-agonists and any controller drugs (for example, theophylline, leukotriene antagonists); intermittent use (less than or equal to 3 uses per week) of inhaled short acting b-agonists was acceptable
- Use of antibiotic therapy for acute conditions within 14 days of screening
- Initiation of immunotherapy during the study period or dose escalation during the study period
- Non-vaccinated exposure to, or active infection with, chickenpox or measles within 21 days of screening
- Exposure to systemic corticosteroids for any indication, chronic or intermittent (for example, contact dermatitis), within 60 days of screening or presence of an underlying condition that could reasonably be expected to require treatment with corticosteroids during the course of the study;
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days prior to screening; use of topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface; or presence of an underlying condition that could reasonably be expected to require treatment with topical corticosteroids during the course of the study
- Use of antiepileptic drugs for epilepsy within 30 days of screening or anytime during the treatment period
- Initiation of pimecrolimus cream 1% or greater or tacrolimus ointment 0.03% or greater during the study

The study treatments were:

1. Ciclesonide nasal spray 50 mg per actuation, two sprays in each nostril in the morning
2. Placebo (vehicle)

Subjects were blinded to treatment allocation and randomised using an interactive voice response system (IVRS). There was a baseline period of 7 to 14 days followed by a treatment period of 12 weeks.

Prohibited medications included: antihistamines, decongestants, cough/cold preparations, vasoconstrictors, major tranquilizers, chromoglycates, tricyclics, other inhaled corticosteroids, systemic corticosteroids, antiepileptic drugs, anti-IgE therapy and/or immunosuppressive drugs.

The efficacy outcome measures were:

- Parent/caregiver assessed reflective TNSS
- PANS
- Rescue medication use (loratadine)

The safety outcome measures were: treatment emergent adverse effects (TEAEs), vital signs, physical examination, ENT findings, serum cortisol concentrations and routine laboratory tests.

Hypothesis tests were performed using ANCOVA. No sample size calculations were performed.

A total of 125 subjects were randomized to treatment; 83 to ciclesonide and 42 to placebo. Of the randomized subjects, 75 (90.4%) in the ciclesonide group and 38 (90.5%) in the placebo group completed the study. The age range was 2.01 to 6.0 years, 50 (56.9%) subjects were female and 53 (43.1%) were male. Excepting that a higher proportion of subjects in the placebo group had historical skin prick tests (52.4% compared with 40.7% in the ciclesonide group), the treatment groups were similar in baseline demographics and disease characteristics.

Over the course of the study there was a statistically significant improvement in reflective TNSS with ciclesonide, of a similar magnitude to that seen in the pivotal studies performed in adults: treatment difference (95% CI) 0.86 (0.13 to 1.60) p = 0.021. The improvements were seen in nasal stuffiness/congestions and in rhinorrhoea but not in nasal itching or sneezing. There was no difference between the treatment groups in PANS. There was no difference between the treatment groups in use of rescue medication.

Study M1-417

Study M1-417 was a multicentre, randomised, double blind, placebo controlled, parallel group study the efficacy, safety and tolerability of intranasally administered ciclesonide 200 mg or 100 mg once daily for 2 weeks in paediatric patients aged 6 to 11 years inclusive. The study was conducted at 69 centres in the US.

The inclusion criteria included:

- Male or female between the ages of 6 and 11 years, inclusive
- General good health
- History of SAR to relevant seasonal allergen (pollen) for a minimum of two years, of sufficient severity to have required treatment (either continuous or intermittent) during this period, and was expected to require treatment for the duration of the study
- Demonstrated sensitivity to a relevant allergen (grass, tree, ragweed and/or relevant fall seasonal allergen [excluding mould]) known to induce SAR through a standard skin prick test
- The positive allergen (pollen) test must have been consistent with the medical history of SAR. The patient was expected to be exposed to the same allergen during the entire duration of their study participation

The exclusion criteria were the same as for Study MI-416 with the inclusion of the following:

- History of alcohol or drug abuse
- Plans to travel outside the study area (the known pollen area for the investigative site) for 24 hours or more during the final 7 days of the baseline period
- Plans to travel outside the study area (the known pollen area for the investigative site) for more than 2 consecutive days or more than 3 days total during the treatment period

The study treatments were:

1. Ciclesonide nasal spray 200 µg/day (50 mg per actuation, two sprays in each nostril in the morning)
2. Ciclesonide nasal spray 100 µg/day (25 mg per actuation, two sprays in each nostril in the morning)
3. Placebo (vehicle)

Subjects were blinded to treatment allocation and block randomised by study site using IVRS. There was a baseline period of 7 to 21 days, followed by a treatment period of 2 weeks (up to 16 days). Prohibited medications included: decongestants, antihistamines, cough and cold preparations, leukotriene antagonists, anticholinergics, tricyclic antidepressants, corticosteroids, azole antifungals, antiepileptic drugs, anti-IgE therapy and/or immunosuppressive drugs.

The primary efficacy outcome measure was the average of AM and PM parent/ caregiver reported reflective TNSS over the 2 weeks of treatment. The secondary efficacy outcome measures were:

- Parent/caregiver reported reflective TNSS and its respective individual nasal symptoms
- Average AM and PM parent/caregiver reported instantaneous TNSS and its respective individual symptoms
- PANS and its respective individual signs and symptoms.

Hypothesis testing was performed using ANCOVA. Multiplicity was addressed by using a sequential approach to hypothesis testing.

The sample size calculation used a SD of 2.4 (from prior data), a power of 90%, a two-sided alpha of 0.05, and a treatment difference of 0.75. This calculation determined that 217 patients per group would be required, and given the short duration of the study few dropouts were anticipated. A final sample size of 220 subjects per treatment group was determined.

A total of 962 subjects were screened and 618 were randomised: 215 to ciclesonide 200 µg, 199 to ciclesonide 100 µg and 204 to placebo. Of the randomised subjects, 588 completed the study: 205 (95.3%) in the ciclesonide 200 µg group, 190 (95.5%) in the ciclesonide 100 µg group and 193 (94.6%) in the placebo group. The age range was 6 to 11 years, 349 (56.5%) subjects were male and 269 (43.5%) were female. The treatment groups were similar in demographic and baseline characteristics. Concomitant medication use was similar for the three treatment groups, except that three subjects in each of the active treatment groups, and none in the placebo group, underwent allergy immunotherapy.

For the primary efficacy outcome measure, the 200 µg dose was superior to placebo but there was no significant difference between the 100 µg dose level and either the 200 µg dose level or placebo (Table 9). However, the effect size for the 300 ug dose compared with placebo was less than that seen in the adult studies: treatment difference (95% CI) 0.39 (0.02 to 0.76) p=0.04. For PANS, ciclesonide 200 µg was superior to placebo [treatment difference (95% CI) 0.92 (0.38 to 1.45) p<0.001] and to 100 µg [treatment difference (95% CI) 0.58 (0.04 to 1.11)] p=0.034 (Table 9). However, there was no significant difference between the 100 µg dose and placebo. For instantaneous TNSS, ciclesonide 200 µg was also superior to placebo: treatment difference (95% CI) 0.37 (0.00 to 0.73) p=0.047 (Table 9). Ciclesonide was superior to placebo for all the individual components of the PANS.

Table 9: Overview of primary and key secondary efficacy analyses – ITT analysis

	Treatment		
	Ciclesonide 200 mcg (N = 215)	Ciclesonide 100 mcg (N = 199)	Placebo (N = 204)
Average of AM and PM parent/caregiver-reported reflective TNSS over the 2-week treatment period			
Baseline			
N	215	199	204
Mean (SD)	8.25 (1.86)	8.41 (1.78)	8.41 (1.81)
Change from Baseline over the 2-week treatment period			
N	215	199	204
LS Mean (SE)	-2.46 (0.13)	-2.38 (0.14)	-2.07 (0.14)
Estimated treatment difference (95% CI) vs placebo	0.39 (0.02, 0.76)	0.32 (-0.06, 0.69)	
p-value[a] vs placebo	0.040	0.103	
Estimated treatment difference (95% CI) vs 100 mcg	0.08 (-0.30, 0.45)		
p-value[a] vs 100 mcg	0.694		
Physician-assessed nasal symptom score at Endpoint			
Baseline			
N	215	199	204
Mean (SD)	7.96 (2.43)	7.73 (2.25)	7.57 (2.46)
Change from Baseline at Endpoint			
N	215	199	204
LS Mean (SE)	-3.30 (0.19)	-2.73 (0.20)	-2.39 (0.20)
Estimated treatment difference (95% CI) vs placebo	0.92 (0.38, 1.45)	0.34 (-0.21, 0.88)	
p-value[b] vs placebo	<0.001	0.223	
Estimated treatment difference (95% CI) vs 100 mcg	0.58 (0.04, 1.11)		
p-value[b] vs 100 mcg	0.034		
Average of AM and PM parent/caregiver-reported instantaneous TNSS over the 2-week treatment period			
Baseline			
N	215	199	204
Mean (SD)	7.46 (2.11)	7.49 (1.98)	7.62 (2.13)
Change from Baseline over the 2-week treatment period			
N	215	199	204
LS Mean (SE)	-2.24 (0.13)	-2.18 (0.13)	-1.87 (0.13)
Estimated treatment difference (95% CI) vs placebo	0.37 (0.00, 0.73)	0.31 (-0.06, 0.68)	
p-value[a] vs placebo	0.047	0.096	
Estimated treatment difference (95% CI) vs 100 mcg	0.05 (-0.31, 0.42)		
p-value[a] vs 100 mcg	0.775		

Study M1-405

Study M1-405 was a randomised, double blind, placebo controlled, single centre, parallel group study of ciclesonide at doses of 200, 100 or 25 µg administered via intranasal spray in children aged 2 to5 years inclusive. The study was conducted at a single centre in the US. The study included male and female patients, in general good health, aged 2 to 5 years,

who had a history of PAR to a relevant perennial allergen for a minimum of 3 months immediately preceding the study. The study treatments were:

1. ciclesonide 200 µg/day (two 50 µg actuations in each nostril once daily)
2. ciclesonide 100 µg/day (one 50 µg actuation in each nostril once daily)
3. ciclesonide 25 µg/day (one 12.5 µg actuation in each nostril once daily)
4. placebo

The study had a 3 to 10 day baseline period, a 6 week treatment period and a 7 day follow up period. The efficacy outcome measures were changes from baseline in reflective 24 hour AM TNSS over 6 weeks of treatment and at selected time points and overall Physician Assessed Nasal Symptom Score (PNSS). Safety outcome measures were: AEs, vital signs, urinary free cortisol, plasma cortisol, clinical laboratory tests. A total of 133 subjects were randomised: 33 to 200 µg, 33 to 100 µg, 33 to 25 µg and 34 to placebo. The age range was 2 to 5 years, 74 (56.1%) subjects were male and 58 (43.9%) were female. There was no significant difference between any of the treatment groups and placebo for any of the efficacy outcome measures.

Additional efficacy data

Study M1-408

Study M1-408 was a single centre, randomised, placebo and active controlled, double blind, parallel group, "non-inferiority" study of the potential additive inhibitory effects on the hypothalamic-pituitary-adrenal axis (HPA-Axis) of ciclesonide nasal spray when administered concomitantly with orally inhaled beclomethasone dipropionate. The study was conducted at a single site in the US. The study included male and female patients, aged 18 to 60 years, with a history of PAR for a minimum of 1 year preceding the screening visit. The study treatments were:

1. Ciclesonide 200 mg intranasal once daily and HPA-beclomethasone dipropionate (BDP) oral inhalation
2. Placebo and HPA-BDP oral inhalation

There was a 10 day screening period, a 10 day run-in period with HPA-BDP, a 43 day treatment period, followed by a single dexamethasone dose and 24 hour cortisol levels. The outcome measures were: serum cortisol, urinary cortisol and AEs. Reflective TNSS was also recorded. A total of 111 subjects were randomised: 56 to ciclesonide and 55 to placebo. Of these subjects 105 completed. Of the randomised subjects, 56 (50.5%) were female, 55 (49.5%) were male, and the age range was 18 to 57 years. The study was not designed primarily as an efficacy study and there was no difference between the treatment groups in reflective TNSS.

Study M1-409

Study M1-409 was a single centre, randomised, placebo and active controlled, double blind, parallel group, non-inferiority study of the potential additive inhibitory effects on HPA-Axis of ciclesonide nasal spray when administered concomitantly with orally inhaled fluticasone propionate/salmeterol. The study was conducted at a single centre in the US. The study included male and female patients, aged 18 to 60 years, with a history of PAR for a minimum of 1 year preceding the screening visit. The study treatments were:

1. Ciclesonide 200 mg intranasal once daily and fluticasone 500 µg / salmeterol 50 µg dry powder for oral inhalation, one actuation twice daily
2. Placebo and fluticasone 500 µg / salmeterol 50 µg dry powder for oral inhalation, one actuation twice daily

There was a 10 day screening period, a 10 day run-in period with fluticasone/salmeterol, and a 43 day treatment period, followed by dexamethasone and 24 hour cortisol levels. Reflective TNSS was also recorded. The outcome measures were serum and urine cortisol, and AEs. A total of 150 subjects were randomised: 75 to ciclesonide and 75 to placebo. Of the randomised subjects, 80 (53.3%) subjects were male, 70 (46.7%) were female, and the age range was 18 to 57 years. The study was not designed primarily as an efficacy study and there was no difference between the treatment groups in reflective TNSS.

Evaluator's overall conclusions on clinical efficacy

Efficacy was demonstrated in adult subjects with both PAR and SAR. In study M1-401, conducted in subjects with SAR, intranasal ciclesonide 200 µg/day showed statistically significant improvements in TNSS but no difference in PANS or RQLQ. In study M1-402, conducted in subjects with PAR, intranasal ciclesonide 200 µg/day showed statistically significant improvement in reflective and instantaneous TNSS and in RQLQ (with improvements in activities, sleep, non-nose/eye symptoms, practical problems and nasal symptoms but not for eye symptoms or the emotional domain) but not in PANS.

The improvement in TNSS with intranasal ciclesonide 200 µg/day has been demonstrated through to 52 weeks in subjects with PAR (Study M1-404).

However the clinical significance of the improvements is not clear, with improvements in TNSS of 9% in SAR (Study M1-401) and 10% in PAR (Study M1-402). This is of particular importance because of the absence of comparator controlled studies. Although ciclesonide may be effective, it may not be as effective as currently available treatments.

The sponsor responded that although no direct head to head studies between Omnaris and other intranasal corticosteroid preparations have been conducted, given the fact that the same composite TNSS score was employed with the other INCS preparations, indirect cross study comparisons can be made. Although it is not appropriate to make definitive conclusions based upon these indirect comparisons, these data support the tenant that the efficacy of Omnaris is within the range of other corticosteroid preparations currently available in the marketplace (see pages 60-61).

In children aged 2 to 5 years with PAR, intranasal ciclesonide 200 µg/day showed improvements in TNSS of a similar magnitude to that seen in adults (Study M1-416). There were improvements in nasal stuffiness/congestion and rhinorrhoea. There was no improvement in PANS and the results were not confirmed by Study M1-405 but that study only included 233 children in the 200 µg dose level. In children aged 6 to 11 years with SAR there were improvements in TNSS and PANS with the 200 µg dose (Study M1-417).

A number of studies demonstrated that the 200 µg/day dose was superior to 100 µg/day but it is not clear whether greater effect would have been achieved at a higher dose level. Study TBN-CL-002 demonstrated in adults with SAR 200 µg/day was superior to 100 µg/day but did not show a plateau of effect. Study M1-403 demonstrated that in children 6 to 11 years of age with PAR there was an increasing effect with increasing dose up to 200 µg/day, with no plateau of effect.

There is some disagreement between studies as to the time to onset of effect. This ranged from 1 hour post dose in Study M1-406 to 12 hours in Study M1-401. Time to onset was 6 hours in Studies M1-407 and M1-413. Study TBN-CL-002 showed effects were apparent from Day 3 of treatment.

Maximal effect was reached at Day 12 in Study M1-401 and Day 37 in Study M1-402.

The use of TNSS was appropriate given the recommendation of this outcome measure in the FDA guidance for development of drugs for allergic rhinitis. However, no validation

studies for this outcome measure were provided. In addition, the sponsor did not formulate a definition of responder and did not perform responder analyses.

The studies were designed and conducted in such a manner that would have ensured exposure to the relevant antigens for PAR and SAR. This included exclusion criteria that restricted movements of study subjects. In addition, the inclusion criteria would have ensured that study subjects were susceptible to relevant antigen exposures during the conduct of the studies.

Safety

Introduction

Safety data for intranasal ciclesonide in the adult and paediatric populations were contained in the submission. In addition the sponsor has performed studies of the effects of ciclesonide on the HPA axis and upon IOP.

Patient exposure

In total 1777 subjects have been exposed to intranasal ciclesonide 200 µg daily (Table 10). This includes 198 subjects under the age of 12 years. The approximate total exposure to ciclesonide 200 µg was 450 patient years and 97 subjects were exposed for one year or more.

Table 10: Patient demographic and other baseline characteristics - all AR studies

Variable	Ciclesonide 200 mcg (N=1777)	Ciclesonide 100 mcg (N=344)	Ciclesonide 50 mcg (N=143)	Ciclesonide 25 mcg (N=348)	Placebo (N=1556)
Age (years)					
Mean (SD)	33 (15)	20 (17)	40 (11)	21 (17)	33 (16)
Median	33	11	40	11	32
Min, Max	2, 75	2, 65	19, 64	2, 64	2, 86
Age Category (n (%))					
< 12 years	198 (11.1%)	199 (57.8%)	0	202 (58.0%)	199 (12.8%)
12-17 years	91 (5.1%)	0	0	0	67 (4.3%)
18-64 years	1457 (82.0%)	144 (41.9%)	143 (100.0%)	146 (42.0%)	1256 (80.7%)
65 years or older	31 (1.7%)	1 (0.3%)	0	0	34 (2.2%)
Gender (n (%))					
Male	730 (41.1%)	172 (50.0%)	38 (26.6%)	150 (43.1%)	641 (41.2%)
Female	1047 (58.9%)	172 (50.0%)	105 (73.4%)	198 (56.9%)	915 (58.8%)
Race[1] (n (%))					
Caucasian	1377 (77.5%)	281 (81.7%)	137 (95.8%)	280 (80.5%)	1217 (78.2%)
Black	218 (12.3%)	47 (13.7%)	5 (3.5%)	46 (13.2%)	188 (12.1%)
Asian	72 (4.1%)	4 (1.2%)	1 (0.7%)	10 (2.9%)	63 (4.0%)
Native American	9 (0.5%)	4 (1.2%)	0	0	9 (0.6%)
Native Hawaiian, or Other Pacific Islander	6 (0.3%)	0	0	1 (0.3%)	2 (0.1%)
Other	95 (5.3%)	8 (2.3%)	0	11 (3.2%)	77 (4.9%)
Ethnicity[2] (n (%))					
Hispanic	275 (15.5%)	70 (20.3%)	40 (28.0%)	74 (21.3%)	239 (15.4%)
Non-Hispanic	1502 (84.5%)	274 (79.7%)	103 (72.0%)	274 (78.7%)	1316 (84.6%)
Smoking History[3] (n (%))					
Never	1011 (70.5%)	N/A	N/A	N/A	823 (68.1%)
Current	159 (11.1%)	N/A	N/A	N/A	135 (11.2%)
Former	265 (18.5%)	N/A	N/A	N/A	251 (20.8%)

SD = Standard deviation

Adverse events

In Study TBN-CL-002 AEs were reported by 176 (24.2%) subjects in total: 32 (22.2%), 38 (26.2%), 39 (27.3%), 36 (24.7%) and 31 (20.9%) subjects in the ciclesonide 200, 100, 50 and 25 µg/day and placebo groups, respectively. The most commonly reported AEs were: increased intraocular pressure (IOP), dizziness, headache, epistaxis, nasal passage irritation and pharyngitis.

In Study M1-403, TEAEs were reported in 116 (70.3%) subjects in the 200 mg/day group, 115 (69.3%) in the 100 mg/day group, 113 (66.9%) in the 25 mg/day group and 109 (66.1%) in the placebo group. The most frequently reported AEs were headache, nasopharyngitis, epistaxis and upper respiratory tract infection (URTI) (Table 11).

Table 11: TEAEs occurring in >2% of patients in either treatment group

Preferred Term[1]	Ciclesonide 200 mcg N=165 n (%)	Ciclesonide 100 mcg N=166 n (%)	Ciclesonide 25 mcg N=169 n (%)	Placebo N=165 n (%)	Total N=665 n (%)
Any Treatment-Related, Treatment-Emergent AE	**116 (70.3%)**	**115 (69.3%)**	**113 (66.9%)**	**109 (66.1%)**	**453 (68.1%)**
Headache	23 (13.9%)	21 (12.7%)	12 (7.1%)	17 (10.3%)	73 (11.0%)
Nasopharyngitis	23 (13.9%)	19 (11.4%)	16 (9.5%)	19 (11.5%)	77 (11.6%)
Epistaxis	14 (8.5%)	15 (9.0%)	13 (7.7%)	16 (9.7%)	58 (8.7%)
Cough	13 (7.9%)	13 (7.8%)	12 (7.1%)	18 (10.9%)	56 (8.4%)
Upper respiratory tract infection	11 (6.7%)	21 (12.7%)	13 (7.7%)	20 (12.1%)	65 (9.8%)
Pharyngolaryngeal pain	11 (6.7%)	15 (9.0%)	9 (5.3%)	10 (6.1%)	45 (6.8%)
Vomiting	9 (5.5%)	11 (6.6%)	8 (4.7%)	8 (4.8%)	36 (5.4%)
Nasal discomfort	7 (4.2%)	6 (3.6%)	8 (4.7%)	3 (1.8%)	24 (3.6%)
Pyrexia	7 (4.2%)	12 (7.2%)	5 (3.0%)	13 (7.9%)	37 (5.6%)
Asthma	6 (3.6%)	7 (4.2%)	3 (1.8%)	8 (4.8%)	24 (3.6%)
Nasal disorder	6 (3.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	7 (1.1%)
Blood potassium increased	5 (3.0%)	2 (1.2%)	1 (0.6%)	0 (0.0%)	8 (1.2%)
Nasal congestion	5 (3.0%)	2 (1.2%)	1 (0.6%)	2 (1.2%)	10 (1.5%)
Rhinitis allergic	5 (3.0%)	1 (0.6%)	5 (3.0%)	2 (1.2%)	13 (2.0%)
Sinusitis	5 (3.0%)	8 (4.8%)	3 (1.8%)	7 (4.2%)	23 (3.5%)
Abdominal pain upper	4 (2.4%)	6 (3.6%)	1 (0.6%)	2 (1.2%)	13 (2.0%)
Ear pain	4 (2.4%)	4 (2.4%)	2 (1.2%)	2 (1.2%)	12 (1.8%)
Hypersensitivity	4 (2.4%)	2 (1.2%)	4 (2.4%)	3 (1.8%)	13 (2.0%)
Influenza	4 (2.4%)	5 (3.0%)	2 (1.2%)	2 (1.2%)	13 (2.0%)
Ear infection	3 (1.8%)	3 (1.8%)	4 (2.4%)	3 (1.8%)	13 (2.0%)
Gastroenteritis viral	3 (1.8%)	3 (1.8%)	5 (3.0%)	3 (1.8%)	14 (2.1%)
Pharyngitis streptococcal	3 (1.8%)	2 (1.2%)	3 (1.8%)	4 (2.4%)	12 (1.8%)
Acute sinusitis	2 (1.2%)	4 (2.4%)	2 (1.2%)	1 (0.6%)	9 (1.4%)
Otitis media	2 (1.2%)	5 (3.0%)	3 (1.8%)	3 (1.8%)	13 (2.0%)
Rash	2 (1.2%)	4 (2.4%)	1 (0.6%)	2 (1.2%)	9 (1.4%)
Urticaria	2 (1.2%)	1 (0.6%)	4 (2.4%)	0 (0.0%)	7 (1.1%)
Gastroenteritis	1 (0.6%)	0 (0.0%)	1 (0.6%)	4 (2.4%)	6 (0.9%)
Nausea	1 (0.6%)	2 (1.2%)	2 (1.2%)	4 (2.4%)	9 (1.4%)
Rhinorrhoea	1 (0.6%)	3 (1.8%)	1 (0.6%)	4 (2.4%)	9 (1.4%)

[1] Preferred Term counts: a patient was counted only once within each Preferred Term.

In Study M1-406, TEAEs were reported in 18 (7.2%) subjects in the ciclesonide group and 36 (14.3%) in the placebo group. The most common TEAE was headache, which occurred in five (2.0%) subjects in the ciclesonide group and ten (4.0%) in the placebo group.

In Study M1-407, TEAEs were reported by 17 (8.1%) subjects in the ciclesonide group and 16 (7.6%) in the placebo group. The most frequently reported TEAE was headache: five (2.4%) subjects in the ciclesonide group and three (1.4%) in the placebo group.

In Study M1-413, TEAEs were reported in 21 (8.2%) subjects in the ciclesonide group and 26 (10.2%) subjects in the placebo group. Epistaxis was reported in 7 (2.7%) subjects in the ciclesonide group and four (1.6%) in the placebo group.

In Study M1-401, 66 (40.2%) subjects in the ciclesonide group and 64 (39.3%) in the placebo group reported TEAEs. The most commonly reported TEAE was nasal passage irritation, occurring in 10 (6.1%) subjects in the ciclesonide group and 9 (5.5%) in the placebo group. Overall, ear and labyrinthine disorders were reported by more subjects in the ciclesonide group: 10 (6.1%) subjects in the ciclesonide group compared with four (2.5%) in the placebo group.

In Study M1-402, TEAEs were reported in 102 (42.9%) subjects in the ciclesonide group and 110 (47.2%) in the placebo group. The most frequently reported AEs were: headache, epistaxis and nasopharyngitis (Table 12). Epistaxis was reported more frequently in the ciclesonide group: 18 (7.6%) compared with 12 (5.2%) in the placebo group.

Table 12: TEAEs reported in ≥0.8% of the ciclesonide group

Preferred term	Ciclesonide 200 mcg (N=238) N (%)	Placebo (N=233) N (%)	Total (N=471) N (%)
Patients with at Least 1 Treatment-Emergent AE	102 (42.9)	110 (47.2)	212 (45.0)
Headache	21 (8.8)	17 (7.3)	38 (8.1)
Epistaxis	18 (7.6)	12 (5.2)	30 (6.4)
Nasopharyngitis	15 (6.3)	16 (6.9)	31 (6.6)
Pharyngitis	9 (3.8)	9 (3.9)	18 (3.8)
Upper respiratory tract infection NOS	8 (3.4)	16 (6.9)	24 (5.1)
Cough	5 (2.1)	5 (2.1)	10 (2.1)
Sinus headache	5 (2.1)	2 (0.9)	7 (1.5)
Ear pain	4 (1.7)	1 (0.4)	5 (1.1)
Insomnia	4 (1.7)	0 (0.0)	4 (0.8)
Rhinitis perennial	4 (1.7)	1 (0.4)	5 (1.1)
Conjunctivitis	3 (1.3)	1 (0.4)	4 (0.8)
Nasal passage irritation	3 (1.3)	5 (2.1)	8 (1.7)
Back pain	2 (0.8)	1 (0.4)	3 (0.6)
Blood pressure increased	2 (0.8)	0 (0.0)	2 (0.4)
Diarrhoea NOS	2 (0.8)	0 (0.0)	2 (0.4)
Dizziness	2 (0.8)	1 (0.4)	3 (0.6)
Dyspepsia	2 (0.8)	0 (0.0)	2 (0.4)
Ear congestion	2 (0.8)	0 (0.0)	2 (0.4)
Headache NOS aggravated	2 (0.8)	2 (0.9)	4 (0.8)
Laboratory test abnormal NOS	2 (0.8)	0 (0.0)	2 (0.4)
Neck pain	2 (0.8)	1 (0.4)	3 (0.6)
Otitis externa NOS	2 (0.8)	0 (0.0)	2 (0.4)
Sinusitis NOS	2 (0.8)	3 (1.3)	5 (1.1)
Throat irritation	2 (0.8)	0 (0.0)	2 (0.4)
Urticaria NOS	2 (0.8)	2 (0.9)	4 (0.8)

In Study M1-404, TEAEs were reported in 331 (75.1%) subjects in the ciclesonide group and 165 (74.3%) in the placebo group. The most commonly reported TEAEs were: URTI, nasopharyngitis, epistaxis, pharyngolaryngeal pain and headache (Table 13).

Table 13: TEAEs reported by >1% of the ciclesonide group

Preferred term	Ciclesonide 200 mcg (N=441) N (%)	Placebo (N=222) N (%)	Total (N=663) N (%)
Patients with at Least 1 Treatment-Emergent AE	331 (75.1)	165 (74.3)	496 (74.8)
Upper respiratory tract infection	72 (16.3)	39 (17.6)	111 (16.7)
Nasopharyngitis	58 (13.2)	40 (18.0)	98 (14.8)
Epistaxis	44 (10.0)	16 (7.2)	60 (9.0)
Pharyngolaryngeal pain	41 (9.3)	10 (4.5)	51 (7.7)
Sinusitis	41 (9.3)	16 (7.2)	57 (8.6)
Headache	33 (7.5)	13 (5.9)	46 (6.9)
Nasal discomfort	20 (4.5)	9 (4.1)	29 (4.4)
Cough	19 (4.3)	5 (2.3)	24 (3.6)
Bronchitis	18 (4.1)	8 (3.6)	26 (3.9)
Influenza	17 (3.9)	8 (3.6)	25 (3.8)
Acute sinusitis	13 (2.9)	9 (4.1)	22 (3.3)
Back pain	13 (2.9)	6 (2.7)	19 (2.9)
Sinus headache	12 (2.7)	7 (3.2)	19 (2.9)
Urinary tract infection	12 (2.7)	2 (0.9)	14 (2.1)
Nausea	10 (2.3)	8 (3.6)	18 (2.7)
Ear pain	9 (2.0)	3 (1.4)	12 (1.8)
Toothache	9 (2.0)	5 (2.3)	14 (2.1)
Gastroenteritis viral	8 (1.8)	2 (0.9)	10 (1.5)
Insomnia	8 (1.8)	4 (1.8)	12 (1.8)
Joint sprain	8 (1.8)	1 (0.5)	9 (1.4)
Migraine	8 (1.8)	3 (1.4)	11 (1.7)
Otitis media	8 (1.8)	2 (0.9)	10 (1.5)
Viral upper respiratory tract infection	8 (1.8)	7 (3.2)	15 (2.3)
Asthma	7 (1.6)	3 (1.4)	10 (1.5)
Diarrhoea	7 (1.6)	5 (2.3)	12 (1.8)
Dizziness	7 (1.6)	1 (0.5)	8 (1.2)
Myalgia	7 (1.6)	4 (1.8)	11 (1.7)
Vomiting	7 (1.6)	2 (0.9)	9 (1.4)
Abdominal pain upper	6 (1.4)	3 (1.4)	9 (1.4)
Dyspepsia	6 (1.4)	2 (0.9)	8 (1.2)
Hypersensitivity	6 (1.4)	5 (2.3)	11 (1.7)
Post procedural pain	6 (1.4)	2 (0.9)	8 (1.2)
Anxiety	5 (1.1)	6 (2.7)	11 (1.7)
Arthralgia	5 (1.1)	3 (1.4)	8 (1.2)
Influenza like illness	5 (1.1)	0 (0.0)	5 (0.8)
Pain in extremity	5 (1.1)	3 (1.4)	8 (1.2)
Pneumonia	5 (1.1)	1 (0.5)	6 (0.9)
Rash	5 (1.1)	1 (0.5)	6 (0.9)
Rhinitis allergic	5 (1.1)	5 (2.3)	10 (1.5)

In Study M1-416, TEAEs were reported by 50 (60.2%) subjects in the ciclesonide group and 23 (54.8%) in the placebo group. The most frequently reported TEAEs were: pyrexia, URTI, cough, otitis media and sinusitis.

In Study M1-417, TEAEs were reported in 27 (12.6%) subjects in the ciclesonide 200 µg/day group, 33 (16.6%) in the 100 µg/day and 39 (19.1%) in the placebo group. The most common TEAEs were epistaxis, headache, asthma and nasal discomfort (Table 14).

Table 14: TEAEs in descending order of frequency in the ciclesonide 200 µg group

Preferred Term	Ciclesonide 200mcg (N=215) N (%)	Ciclesonide 100mcg (N=199) N (%)	Placebo (N=204) N (%)	Total (N=618) N (%)
Patients With at Least 1 AE	27 (12.6)	33 (16.6)	39 (19.1)	99 (16.0)
Epistaxis	3 (1.4)	7 (3.5)	8 (3.9)	18 (2.9)
Ear pain	2 (0.9)	2 (1.0)	1 (0.5)	5 (0.8)
Headache	2 (0.9)	4 (2.0)	4 (2.0)	10 (1.6)
Nasopharyngitis	2 (0.9)	0 (0.0)	1 (0.5)	3 (0.5)
Pharyngolaryngeal pain	2 (0.9)	2 (1.0)	2 (1.0)	6 (1.0)
Upper respiratory tract infection	2 (0.9)	1 (0.5)	2 (1.0)	5 (0.8)
Abdominal pain upper	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Asthma	1 (0.5)	1 (0.5)	4 (2.0)	6 (1.0)
Conjunctivitis infective	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Conjunctivitis viral	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Contusion	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Cough	1 (0.5)	0 (0.0)	2 (1.0)	3 (0.5)
Exposure to toxic agent	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Eye disorder	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Hypersensitivity	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Injury	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)
Nasal discomfort	1 (0.5)	1 (0.5)	7 (3.4)	9 (1.5)
Nasal dryness	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Oedema mucosal	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Oral pain	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Otitis externa	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Parosmia	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Pyrexia	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Sinusitis	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Urticaria	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Varicella	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)
Vomiting	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Abdominal pain	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Aphthous stomatitis	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Arthropod sting	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Chest pain	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Conjunctival hyperaemia	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Conjunctivitis allergic	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Constipation	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Dermatitis atopic	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Dermatitis contact	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Dizziness	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Excoriation	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Gastroenteritis viral	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)
Hyperventilation	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Joint sprain	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Localised infection	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Motion sickness	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Muscle spasms	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Nasal disorder	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Nasal mucosal disorder	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Nasal oedema	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Nasal septum disorder	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Periorbital oedema	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Procedural pain	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Rash	0 (0.0)	2 (1.0)	1 (0.5)	3 (0.5)
Sinus operation	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Throat irritation	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Urinary tract infection	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)
Viral infection	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)

In Study M1-405, TEAEs were reported in six (18.2%) subjects in the 200 µg/day group, eight (24.2%) in the 100 µg/day, seven (21.2%) in the 25 µg/day and nine (26.5%) in the placebo group. There was no pattern in the AEs. There were no changes in IOP.

In Study M1-408, TEAEs were reported in 32 (57.1%) subjects in the ciclesonide group and 33 (60.0%) in the placebo group. The most common TEAE was increased systolic blood pressure which occurred in seven (12.5%) subjects in the ciclesonide group and seven (12.7%) in the placebo group.

In Study M1-409, TEAEs were reported in 20 (26.7%) subjects in the ciclesonide group and 17 (22.7%) in the placebo group. The most frequently reported TEAE was headache: four (5.3%) subjects in the ciclesonide group and six (8.0%) in the placebo group.

In the sponsor's *Integrated Summary of Safety* the most common TEAEs with intranasal ciclesonide 200 µg daily were headache (6.0%), nasopharyngitis (5.9%) and epistaxis (5.1%) (Table 15).

Table 15: TEAEs occurring in at least 2% of patients in any treatment group (number (%) of patients) - all AR studies

Preferred Term	Ciclesonide 200 mcg (N=1777)	Ciclesonide 100 mcg (N=344)	Ciclesonide 50 mcg (N=143)	Ciclesonide 25 mcg (N=348)	Placebo (N=1556)
Mean treatment exposure (days)	**92.4**	**49.2**	**14.7**	**47.7**	**64.2**
Patients with one or more treatment-emergent AEs	**740 (41.6%)**	**161 (46.8%)**	**39 (27.3%)**	**156 (44.8%)**	**589 (37.9%)**
Headache	106 (6.0%)	23 (6.7%)	6 (4.2%)	15 (4.3%)	81 (5.2%)
Nasopharyngitis	104 (5.9%)	21 (6.1%)	0	19 (5.5%)	83 (5.3%)
Epistaxis	91 (5.1%)	19 (5.5%)	3 (2.1%)	16 (4.6%)	59 (3.8%)
Upper respiratory tract infection	84 (4.7%)	21 (6.1%)	0	13 (3.7%)	60 (3.9%)
Pharyngolaryngeal pain	54 (3.0%)	15 (4.4%)	0	9 (2.6%)	24 (1.5%)
Sinusitis	47 (2.6%)	8 (2.3%)	0	3 (0.9%)	24 (1.5%)
Cough	45 (2.5%)	14 (4.1%)	1 (0.7%)	13 (3.7%)	33 (2.1%)
Nasal discomfort	27 (1.5%)	6 (1.7%)	0	8 (2.3%)	14 (0.9%)
Pharyngitis	24 (1.4%)	7 (2.0%)	1 (0.7%)	5 (1.4%)	28 (1.8%)
Influenza	23 (1.3%)	7 (2.0%)	0	3 (0.9%)	13 (0.8%)
Vomiting	16 (0.9%)	11 (3.2%)	0	8 (2.3%)	10 (0.6%)
Asthma	14 (0.8%)	7 (2.0%)	0	3 (0.9%)	11 (0.7%)
Pyrexia	13 (0.7%)	14 (4.1%)	2 (1.4%)	7 (2.0%)	21 (1.3%)
Abdominal pain upper	12 (0.7%)	7 (2.0%)	0	1 (0.3%)	5 (0.3%)
Intraocular pressure increased	8 (0.5%)	7 (2.0%)	6 (4.2%)	11 (3.2%)	7 (0.4%)

Serious adverse events and deaths

In Study TBN-CL-002, SAEs were reported by two (1.4%) subjects in the ciclesonide 100 mg/day group only (motor vehicle accident and diverticulitis).

In Study M1-403, SAEs were reported in two (1.2%) subjects in the 200 mg/day group (viral gastroenteritis and abdominal pain) and one (0.6%) in the placebo group (skull fracture).

In Study M1-401, one (0.6%) subject in the ciclesonide group reported a SAE (increased heart rate).

In Study M1-404, SAEs were reported in 16 (3.6%) in the ciclesonide group and six (2.7%) in the placebo group. Four of the SAEs in the ciclesonide group related to depression, suicidal ideation or drug overdose.

In Study M1-417, SAEs were reported in one subject in each of the ciclesonide 200 µg/day and 100 µg/day groups. The SAEs were two deaths, both as a result of the same motor vehicle accident.

In Study M1-405, there was one SAE in the 25 µg/day group (febrile illness).

There were no SAEs reported in Studies M1-406, M1-407, M1-413, M1-402, M1-406, M1-408 or M1-409.

There were no deaths reported during Study M1-403, Study M1-406, Study M1-407, Study M1-403, Study M1-401, Study M1-402, Study M1-404, Study M1-406, M1-405, M1-408 or M1-409.

Laboratory findings

In Study TBN-CL-002 two subjects had elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which had not resolved by the study end.

In Study M1-403, there were no clinically significant abnormalities in laboratory values. There were no significant differences between the treatment groups for the change from baseline in plasma cortisol concentrations. There were no significant differences between the groups in mean IOP.

In Study M1-401, there was a slightly higher rate of eosinophilia in the ciclesonide group, seven (4.5%) subjects compared with four (2.6%) in the placebo group. Apart from this, the pattern of abnormal laboratory results was similar for the two groups.

In Study M1-402, shifts to abnormal laboratory values occurred to a similar extent in both treatment groups.

In Study M1-404, a higher proportion of subjects in the ciclesonide group had elevations in ALT: 19 (5.2%) subjects compared with five (2.9%) in the placebo group. Other than this there were no meaningful differences in the pattern of abnormal laboratory test results.

In Study M1-416 abnormalities in haematology parameters followed a similar pattern for both treatment groups. However, in the ciclesonide group, 15 (25.0%) subjects developed elevated calcium concentrations, six (8.1%) developed elevated lipase concentrations and eight (12.7%) developed elevated phosphate concentrations.

In Study M1-405, urinary free cortisol decreased to a greater extent in the ciclesonide groups compared with placebo but the differences were not statistically significant. In a similar manner, plasma cortisol concentrations also decreased to a greater extent in the ciclesonide groups and the differences were not statistically significant. Only three (1.1%) of 285 plasma samples obtained from ciclesonide treated patients demonstrated detectable levels of ciclesonide.

In Study M1-408, there was no difference between the treatment groups in serum or urinary cortisol.

In Study M1-409, there was no difference between the treatment groups in plasma or urinary cortisol.

There were no laboratory AEs reported for Studies M1-406 and M1-407. In Study M1-417, clinical laboratory evaluations were not performed in the study.

The *Integrated Summary of Safety* indicated that there was no difference between intranasal ciclesonide 200 µg daily and placebo in IOP.

Safety in special populations

Overall, the rate of TEAEs in subjects less than 12 years age with intranasal ciclesonide 200 µg daily was similar to that for placebo, as was the pattern of TEAEs. These TEAEs were primarily related to the upper respiratory tract.

SAEs were rare in paediatric patients and did not appear to be related to the treatment.

The *Integrated Summary of Safety* stated that no studies assessing the effect of ciclesonide nasal spray on growth have been conducted.

Discontinuation due to adverse events

In Study TBN-CL-002 seven subjects discontinued because of AEs, the greatest number (three) being in the 100 mg/day group.

In Study M1-403, AEs leading to discontinuation occurred in three (1.8%) subjects in the 200 mg/day group, five (3.0%) in the 100 mg/day group, four (2.4%) in the 25 mg/day group and ten (6.1%) in the placebo group.

In Study M1-407, AEs resulted in discontinuation in 2 (1%) subjects in the ciclesonide group (nausea and hypoesthesia) and 1 (0.5%) in the placebo group (pharyngolaryngeal pain).

In Study M1-413 there was one discontinuation due to AE in the placebo group (allergic conjunctivitis).

In Study M1-401, four (2.4%) subjects in the ciclesonide group discontinued because of an AE, compared with five (3.1%) in the placebo group. These AEs were predominantly upper or lower respiratory in nature, but no individual events were reported in more than one discontinuing subject.

In Study M1-402, ten (4.2%) subjects in the ciclesonide group and eleven (4.7%) in the placebo group discontinued because of an AE. The AEs leading to discontinuation were predominantly upper and lower respiratory tract ailments.

In Study M1-404, discontinuation due to AE occurred for 19 (4.3%) subjects in the ciclesonide group and six (2.7%) in the placebo group. Two (0.5%) subjects in the ciclesonide group discontinued because of epistaxis.

In Study M1-416, discontinuation because of AE occurred for two (2.4%) subjects in the ciclesonide group (headache/dizziness, burning sensation in nose and eyes) and one (2.4%) in the placebo group (skin rash).

In Study M1-417, discontinuation due to AEs were reported in three (1.4%) subjects in the ciclesonide 200 µg group, five (2.5%) in the 100 µg group and six (2.9%) in the placebo group. In the ciclesonide groups, there was no clear pattern of AEs leading to discontinuation.

In Study M1-408, there were two discontinuations due to AEs in the ciclesonide group: influenza and influenza-like illness.

In Study M1-409, one (1.3%) subject in the ciclesonide group (sinusitis) and two (2.7%) in the placebo group (bronchitis, dental caries) discontinued because of AEs.

There were no discontinuations due to AEs in Study M1-406 or Study M1-405.

The *Integrated Summary of Safety* indicated that overall the most common reasons for discontinuation were asthma (0.2%) and epistaxis (0.2%). However, the incidence of discontinuation for these reasons was similar for the intranasal ciclesonide 200 µg group as for placebo.

Evaluator's overall conclusions on clinical safety

The TEAEs occurring with intranasal ciclesonide were similar to those events associated with SAR and PAR: headache, epistaxis and nasopharyngitis. The incidence of TEAEs was also similar for the treatment and placebo groups. SAEs were uncommon and appeared to be unrelated to study treatment. There was no clear pattern of AEs leading to discontinuation. There was no pattern of laboratory abnormalities relating to treatment. Intranasal ciclesonide did not appear to have significant effects upon the HPA axis or upon IOP. Hence intranasal ciclesonide appears to be well tolerated and to have a good safety profile.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacodynamics

Were studies comparing intranasal ciclesonide 200 mg with 400 mg performed? Were there clear reasons for choosing the 200 mg dose level in preference to a higher dose level?

Efficacy

Efficacy data were presented demonstrating efficacy for PAR in children aged 2 to 5 years. Why is this age group not contained in the proposed indications? The PI states that there are safety data in children aged 2 to 12 years. This might encourage off-label use. Hence it would be important for prescribers to have access to efficacy data in this population.

Were any studies conducted using active comparator?

What is the clinical significance of the treatment effect?

Clinical Summary and Conclusions

Clinical aspects

Ciclesonide has been developed as a topical corticosteroid for respiratory conditions. Its potential advantages are reduced systemic exposure to exogenous corticosteroid in the treatment of PAR and SAR. This could potentially reduce the risks of growth failure, bone demineralisation and ocular side effects. However, the efficacy of ciclesonide in SAR and PAR has not been compared to active comparator and the clinical significance of the therapeutic effect is not clear.

Benefit risk assessment

Benefits

Efficacy was demonstrated in adult subjects with both PAR and SAR. In study M1-401, conducted in subjects with SAR, intranasal ciclesonide 200 µg/day showed statistically significant improvements in TNSS but no difference in PANS or RQLQ. In study M1-402, conducted in subjects with PAR, intranasal ciclesonide 200 µg/day showed statistically significant improvement in reflective and instantaneous TNSS and in RQLQ (with improvements in activities, sleep, non-nose/eye symptoms, practical problems and nasal symptoms, but not for eye symptoms or the emotional domain) but not in PANS.

The improvement in TNSS with intranasal ciclesonide 200 µg/day has been demonstrated through to 52 weeks in subjects with PAR (Study M1-404).

However the clinical significance of the improvements is not clear, with improvements in TNSS of 9% in SAR (Study M1-401) and 10% in PAR (Study M1-402). This is of particular

importance because of the absence of comparator controlled studies. Although ciclesonide may be effective, it may not be as effective as currently available treatments.

As previously noted, the sponsor responded that although no direct head to head studies between Omnaris and other intranasal corticosteroid preparations have been conducted, given the fact that the same composite TNSS score was employed with the other INCS preparations, indirect cross study comparisons can be made. Although it is not appropriate to make definitive conclusions based upon these indirect comparisons, these data support the tenant that the efficacy of Omnaris is within the range of other corticosteroid preparations currently available in the marketplace (see pages 60-61).

In children aged 2 to 5 years with PAR, intranasal ciclesonide 200 µg/day showed improvements in TNSS of a similar magnitude to that seen in adults (Study M1-416). There were improvements in nasal stuffiness/congestion and rhinorrhoea. There was no improvement in PANS, and the results were not confirmed by Study M1-405 but that study only included 233 children in the 200 µg dose level. In children aged 6 to 11 years with SAR there were improvements in TNSS and PANS with the 200 µg dose (Study M1-417).

A number of studies demonstrated that the 200 µg/day dose was superior to 100 µg/day, but it is not clear whether greater effect would have been achieved at a higher dose level. Study TBN-CL-002 demonstrated in adults with SAR 200 µg/day was superior to 100 µg/day but did not show a plateau of effect. Study M1-403 demonstrated that in children 6 to 11 years of age with PAR there was an increasing effect with increasing dose up to 200 µg/day, with no plateau of effect.

There is some disagreement between studies as to the time to onset of effect. This ranged from 1 hour post dose in Study M1-406 to 12 hours in Study M1-401. Time to onset was 6 hours in Studies M1-407 and M1-413. Study TBN-CL-002 showed effects were apparent from Day 3 of treatment.

Maximal effect was reached at Day 12 in Study M1-401 and Day 37 in Study M1-402.

The design of the clinical studies conformed to the TGA-adopted EU guideline.[3] The use of TNSS was appropriate given the recommendation of this outcome measure in the FDA guidance for development of drugs for allergic rhinitis. However, no validation studies for this outcome measure were provided. In addition, the sponsor did not formulate a definition of responder and did not perform responder analyses.

Risks

The TEAEs occurring with intranasal ciclesonide were similar to those events associated with SAR and PAR: headache, epistaxis and nasopharyngitis. The incidence of TEAEs was also similar for the treatment and placebo groups. SAEs were uncommon and appeared to be unrelated to study treatment. There was no clear pattern of AEs leading to discontinuation. There was no pattern of laboratory abnormalities relating to treatment. Intranasal ciclesonide did not appear to have significant effects upon the HPA axis or upon IOP. Hence intranasal ciclesonide appears to be well tolerated and to have a good safety profile.

Balance

Intranasal ciclesonide has a favourable safety profile, so notwithstanding that the clinical significance of the treatment effect is not clear, the risk benefit assessment is in favour of ciclesonide.

[3] EMEA, Committee for Medicinal Products for Human Use (CHMP), 21 October 2004. Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-conjunctivitis, CPMP/EWP/2455/02.

Conclusions

Ciclesonide should be approved for the following indications:

For the treatment of seasonal allergic rhinitis in adults and children 6 years of age and older.

For the treatment of perennial allergic rhinitis in adults and adolescents 12 years of age and older.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 16.

Table 16: Summary of ongoing safety concerns

Important identified risks	Hypersensitivity reactions
Important potential risks	HPA-axis supression Decreased bone density Effects on growth in children Eye disorders Skin bruising Local otorhinolaryngeal effects
Important missing information	The in-depth analysis of safety data presented above pertaining to potential risks provides a broad overview of the safety profile of ciclesonide. However, there is only limited or no information from clinical trials in the following subgroup: – Pregnant and breast-feeding women

OPR comments on the RMP Safety Specification

The reviewer noted that the summary of the Ongoing Safety Concerns as specified by the sponsor was acceptable.

Pharmacovigilance Activities

The sponsor stated that continuous monitoring by routine pharmacovigilance practices are sufficient for all the specified ongoing safety concerns and no additional actions are planned.[4]

[4] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The evaluation of the nonclinical and clinical aspects of the RMP appears to confirm that intranasal ciclesonide is well tolerated and has a good safety profile. Therefore this was considered acceptable.

Risk Minimisation Activities

The sponsor stated that based on the current safety profile of ciclesonide, no risk minimisation activities other than routine risk minimisation activities are considered necessary at this point.[5] This was considered acceptable.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator noted that ciclesonide is a steroidal prodrug which is closely related structurally to budesonide. Ciclesonide contains nine chiral centres but is presented as a single enantiomer. The aqueous suspension is hypotonic.

There were no outstanding chemistry and quality control issues. Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

The application was referred to the PSC. The subcommittee recommended that registration subject to a correction to the Consumer Medicines Information (CMI) document. The PSC was of the view that the systemic bioavailability of ciclesonide from the proposed nasal suspension was significantly lower than from the currently registered product that is used for asthma.

Nonclinical

The evaluator stated that nonclinical data were 'sufficiently comprehensive and of high quality'. A major pharmacologically active metabolite of ciclesonide is des-ciclesonide (RM1). *In vitro* studies showed inhibition of cytokine release by human nasal epithelial cells. There was significant and long lasting inhibition on nasal blockage and eosinophilic infiltration in the guinea pig model of allergic rhinitis.

The evaluator also noted the conversion of ciclesonide to RM1 in human and animal nasal epithelial cells in *in vitro* studies. RM1 has more potent pharmacological actions than ciclesonide. Systemic absorption following intranasal administration of ciclesonide was limited in humans, rats and dogs. Similarly, negligible levels of RM1 were detected in the same species. Clinical studies comparing intranasal vs inhalation of ciclesonide showed significantly less absorption with intranasal use.

Repeat dose toxicity studies by the intranasal route were conducted in rats (up to 4 weeks) and dogs (up to 6 weeks). Higher strengths and more frequent dosing schedules than those proposed in humans were employed in these studies. There was no mucosal irritation seen. Local and systemic findings are consistent with corticosteroid activity, however there were substantial dose multiples at the NOELs suggesting limited clinical relevance.

The evaluator recommended approval on nonclinical grounds.

[5] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Clinical

Pharmacokinetics/Pharmacodynamics

Pharmacokinetics

Study M1-422 assessed the systemic exposure of des-ciclesonide after ciclesonide nasal spray (300 µg), hydrofluoroalkane (HFA) nasal aerosol (300 µg) and orally inhaled ciclesonide (320 µg) in 30 healthy adults. The systemic exposure was lower for the aqueous spray than for HFA nasal spray or orally inhaled ciclesonide. The quality evaluator reached similar conclusions.

Study TBN-CL-001 assessed the pharmacokinetics after multiple doses in healthy and asymptomatic seasonal allergic rhinitis (SAR) subjects. Since the majority were below the limit of quantification the pharmacokinetics was not calculated. The evaluator noted that there was no difference in serum cortisol profiles.

Interactions

The interaction with formoterol was assessed in Study CP-029. It was an open randomised three period crossover study on 24 healthy volunteers. Systemic exposure of ciclesonide decreased in combination with formoterol but the evaluator was of the opinion that the decrease in formoterol was not clinically significant.

The interaction with ketoconazole was assessed in Study CP-036 which was a steady state study that assessed the pharmacokinetics of orally inhaled ciclesonide and its active metabolite with or without CYP3A4 enzyme inhibition. There was a 3.5 fold increase of RM1 metabolite. There was no increase in parent ciclesonide exposure.

Population pharmacokinetics

The evaluator also noted a population pharmacokinetic analysis of the Phase I studies involving 151 subjects that examined the pharmacokinetics and pharmacodynamics of RM1 (metabolite of ciclesonide) and the effect of serum cortisol concentration. It was noted that the RM1 volume of distribution was affected by weight; there was no effect on ciclesonide dose on cortisol AUC.

Pharmacodynamics

One study FHP012 examined the pharmacodynamic effect of ciclesonide on endogenous cortisol concentration. This was an open, placebo controlled, two period, crossover study that compared ciclesonide vs budesonide following repeat dose inhalations in 12 healthy male volunteers. There was no significant difference on ACTH stimulation of cortisol: 1.06 (95% CI: 0.99, 1.15).

Studies conducted in environmental exposure chambers (EEC)

Three studies MI-406, MI-407 and MI-413 were submitted. All three studies were of similar design. They were double blind randomised placebo controlled single centre parallel group studies conducted in an EEC chamber in patients over the age of 18 with SAR, with sensitivity to short ragweed. The primary efficacy outcome measure was the time to onset of action measured by a difference between ciclesonide and placebo in the change from baseline in patient assessed instantaneous TNSS.

In study 406, there was a statistically significant difference in relation to the primary outcome measure, at 1 hour and this persisted for 12 hours (Table 4). In study 407, statistically significant difference was seen at 6 and 7 hours and not at other time points; hence, onset of action could not be verified in this study (Table 5). In study 413, statistically significant difference was seen at 6, 7, 9, 10 and 11 hours (Table 6). These findings need to be confirmed with field studies.

Dose ranging studies

There were two dose ranging studies submitted (TBN-CL-002 and MI-402).

Study TBN-CL-002 was a multicentre, double blind, randomised, placebo controlled parallel group study in patients with SAR. Those with a two year history of SAR (as assessed by the physician) and experiencing a minimum of 8 of the total nasal symptoms score and a maximum of 12, for at least 3 days in the screening phase were eligible to participate.

The primary efficacy endpoint was reflective patient scoring of four nasal symptoms, reflective total nasal symptom score (rTNSS), (rhinorrhoea, nasal congestion, nasal itching and sneezing) twice daily (AM and PM) on a four point scale (0=absent, 1=mild, 2=moderate and 3 = severe). The secondary endpoints included the patient's and investigator's global evaluation, instantaneous TNSS, AUC of reflective TNSS, individual reflective symptom scores and rescue medication use.

There was a significant improvement in TNSS for both the 100 µg/day and 200 µg/day doses in relation to primary efficacy endpoints (Table 2). Secondary endpoints (other than rescue medication) generally reflected these findings. There were no significant differences between the groups in relation to rescue medication.

Study M1 403 was a Phase III study on 6-11 year olds with Perennial Allergic Rhinitis (PAR). This is also a double blind randomised placebo controlled study using 25 µg, 100 µg or 200 µg ciclesonide daily. History of PAR to a relevant allergen for a minimum 6 months was required.

The primary efficacy endpoint was the average AM and PM caregiver/ patient reported reflective TNSS over the first six weeks of treatment. Several TNSS indices were also included as secondary endpoints.

For the primary efficacy outcome variable, there was no significant difference between any of the treatment groups and placebo (Table 3). However, there did appear to be a treatment effect with increasing dose.

Efficacy

Pivotal studies

SAR in adolescents and adults - Study 401.

Study 401 was a double blind placebo controlled parallel group study in those with a history of SAR and positive sensitivity to Mountain Cedar Pollen by skin test.

The primary efficacy outcome measure was the average of AM and PM patient assessed reflective TNSS over the first two weeks of treatment. Secondary efficacy endpoints included various TNSS indices, physician's scores, quality of life measures and time to onset of action.

The changes were observed in relation to the AM+PM reflective TNSS (primary) and instantaneous TNSS (secondary) endpoint are shown in Table 17 (see also Table 7).

Table 17: Changes from placebo in Study 401

Treatment	n	Baseline	Change from baseline	Difference from placebo		
				Estimate	95% CI	p value
Reflective TNSS, AM+PM score						
ciclesonide	162	8.96	-2.40	-0.90	(-1.36,-0.45)	<0.01
placebo	162	8.83	-1.50			
Instantaneous, AM+PM score						
ciclesonide	162	8.40	-2.15	-0.87	(-1.31,-0.44)	<0.01
placebo	162	8.33	-1.28			
Instantaneous TNSS, AM score						
Ciclesonide	162	8.45	-1.87	-0.84	(-1.30,-0.39)	<0.01
Placebo	162	8.33	-1.03			

Other secondary endpoints were discussed. Some endpoints relating to quality of life and physicians' scores were not significantly different.

PAR in adolescents and adults - Study 402.

Study 402 was also a double blind placebo controlled parallel group study on patients 12 years and older with history of PAR and positive sensitivity to relevant allergen by skin test. The primary endpoint was similar to the previous study but was assessed after 6 weeks of treatment.

Results obtained are shown in Table 18 (see also Table 8).

Table 18: Changes from placebo in Study 402

Treatment	n	Baseline	Change from baseline	Difference from placebo		
				Estimate	95% CI	p value
Reflective TNSS, AM+PM score						
ciclesonide	232	7.59	-2.51	-0.62	(-0.97,-0.28)	<0.01
placebo	229	7.72	-1.89			
Instantaneous, AM+PM score						
ciclesonide	232	7.07	-2.21	-0.53	(-0.87,-0.20)	<0.01
placebo	229	7.09	-1.68			
Instantaneous TNSS, AM score						
Ciclesonide	232	7.05	-1.99	-0.53	(-0.90,-0.17)	<0.01
Placebo	229	7.05	-1.46			

The evaluator noted that improvement in reflective TNSS occurred during all time intervals during treatment. However, the magnitude of difference was small "with at best a 10% improvement with ciclesonide". Both AM and PM scores showed improvement. Generally no clinically significant changes regarding quality of life measures, physicians' questionnaires were seen. In relation to individual symptoms there was improvement with itching, sneezing, runny nose but not with congestion.

Studies in children

SAR - Study M1-417

Study M1-417 was a multicentre randomised double blind placebo controlled parallel group study of ciclesonide 100 µg or 200 µg/day for two weeks in paediatric patients 6 to 11 years. History of SAR to relevant allergen (pollen) for a minimum of 2 years of sufficient severity was required.

The primary efficacy outcome measure was the average of AM+PM parent/caregiver reported reflective TNSS over two weeks. Other aspects of TNSS were secondary efficacy variables.

The evaluator noted that for the primary efficacy outcome measure, the 200 µg dose was superior to placebo, but there was no significant difference between the 100 µg dose level and the 200 µg dose level; there was no significant difference between the 100 µg dose level and placebo. The effect size was smaller than that seen in the adult studies.

PAR

These studies were of limited relevance as approval was not sought for PAR in children.

Study M1-416 was a multicentre double blind placebo controlled study of 12 weeks duration in paediatric patients (2-5 years) with PAR. A positive allergen test which was consistent with the medical history of PAR was required. The evaluator noted that, over the course of the study, there was a statistically significant improvement in reflective TNSS with ciclesonide, of a similar magnitude to that seen in the pivotal studies performed in adults: treatment difference (95% CI) -0.86 (-0.13 to -1.60) p = 0.021.

Study M1-405 was a study similar in design to the above mentioned study on children 2-5 years old, using three different doses of ciclesonide (25, 100 or 200 µg/day) for 6 weeks vs

placebo. There were no significant difference between treatment groups in reflective 24-hour AM TNSS (efficacy outcome measure).

Additional efficacy data

The evaluator briefly discussed two studies MI-408 and MI-409 which were studies that essentially assessed the effects of ciclesonide on HPA axis. Thus, they were not designed primarily as efficacy studies and will not be considered to support efficacy.

Safety

The evaluator noted that 1,777 subjects were exposed to intranasal 200 µg daily; of these, 198 subjects were under 12 years of age. A total of 97 subjects were exposed for one year or more. The evaluator noted that the most common treatment emergent adverse events (TEAEs) with intranasal ciclesonide 200 µg/day were headache (6%), nasopharyngitis (5.9%) and epistaxis (5.1%).

Of the serious adverse events, the evaluator reported 4 events that related to depression, suicidal ideation or drug overdose. Overall, the SAEs did not reveal any trends as they were isolated events.

The evaluator also noted that the TEAEs in subjects less than 12 years were similar between active and placebo groups. No studies assessing the effect of ciclesonide nasal spray on growth have been conducted.

Overall the most common reasons for discontinuation were asthma (0.2%) and epistaxis (0.2%). However, the incidence of discontinuation for these reasons was similar for the intranasal ciclesonide 200 µg group as for placebo.

The effect on HPA axis was not discussed by the evaluator. The following information has been obtained from the submission and from the US FDA medical review accessed on the FDA website. Though no significant effect was seen, the studies generally lacked rigour in collecting specimens and in monitoring to be meaningful.

Long term effects were assessed in study 404**:** 441 patients were exposed to ciclesonide and 222 to placebo; here 353 subjects were treated for 6 months and 97 were treated for 12 months. Adverse events were reported in similar frequency to placebo. They were similar to those reported in the short term studies except for the following TEAEs of note: candidiasis (1) and increased IOP (1). Of the SAEs, there were four reports of suicidal ideation in the ciclesonide group (3 of the 4 were on chronic treatment for psychiatric disorders; 3 reports of pneumonia (2 had a past history of asthma). All recovered except one patient with pneumonia who discontinued.

Intraocular pressure was measured in studies 403, 404 and 405. Baseline and endpoint measurements were done in 639 patients who were treated with 200 µg ciclesonide. Small changes were seen and these were similar in the ciclesonide and placebo groups.

Visual acuity and slit lamp examination did not reveal any significant difference between groups relating to lens opacity.

Overall conclusions of the evaluator

Overall, the evaluator concluded that there was an acceptable risk benefit profile and recommends approval. However, the following points were noted.

- The clinical significance of the improvements is not clear. Improvements in TNSS of 9% in SAR (Study M1-401) and 10% in PAR (Study M1-402) were observed and the relevance of this in the absence of an active comparator is not clear.

- "A number of studies demonstrated that the 200 µg/day dose was superior to100µg/day but it is not clear whether greater effect would have been achieved at a higher dose level".
- The time to onset of effect is unclear. It ranged from 1 hour post dose in Study M1-406 to 12 hours in Study M1-401. Time to onset was 6 hours in Studies M1-407 and M1-413. Study TBN-CL-002 showed effects were apparent from Day 3 of treatment.
- Though the studies generally conformed to TGA-adopted EU guidelines, no validation studies on the outcome measure TNSS are submitted.[3] Similarly the sponsor has not provided any form of responder analysis.

Sponsor's response:

The Delegate noted that the sponsor addressed the lack of active comparators in the submission by cross study comparison with inhaled corticosteroids.

Risk Management Plan

The Risk Management Plan has been evaluated by the Office of Product Review. There was a need for finalisation of details concerning the product information and labels/packaging to realise routine risk minimisation measures.

Risk-Benefit Analysis

Delegate Considerations

1. The efficacy of this product is only established against placebo and the absolute effect size is rather small, even in adults.
2. The lack of active comparators is a significant deficiency.
3. The maintenance of efficacy for these indications or whether the use of this agent prevents relapses in PAR is not known. This may cause some concern in regard to the approvability of Omnaris in PAR.
4. No specific safety concerns arise from this data package.

The Delegate proposed that the application be approved.

Response from Sponsor

The sponsor agreed with the Delegate's proposed action that Omnaris should be approved for the following indications:

For the treatment or seasonal allergic rhinitis (SAR) in adults and children 6 years of age and older; and for the treatment of perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older.

The sponsor provided a number of comments which related to the proposed product information (PI) but these are beyond the scope of this AusPAR. The sponsor also recognised that there was a need to finalise the PI in order to realise the risk minimisation measures outlined in the Risk Management Plan (RMP). At the time of this response the sponsor was in the process of modifying the RMP in line with TGA recommendations. The RMP is a global document and requires input from various global teams in order to agree on amendments. The RMP would be finalised following the ACPM meeting where the sponsor indicated it would be happy to consider any additional recommendations proposed by the TGA prior to product approval.

Efficacy

The FDA guidance states that the preferred measures to assess the effectiveness of agents under development for the use in AR are patient self-rated instantaneous and reflective

composite symptom scores [FDA, 2000].[6] The sponsor utilised this composite symptom score in the development of Omnaris and employed the change in average AM and PM 12 hour reflective total nasal symptom score (TNSS) ratings as the primary measure of treatment efficacy in the pivotal studies. The TNSS score was obtained by summing the nasal congestion, nasal itching, rhinorrhoea, and sneezing scores each rated on a 0-3 severity scale.

TNSS use is widespread and TNSS results have been reported extensively to support efficacy and subsequent marketing applications globally, as well as in Australia, for effective agents used to treat allergic rhinitis [for example, Avamys, Australian Product Information, March 2009].

The use of TNSS to measure a clinically important difference has been analysed in great detail by Barnes (2006).[7] Barnes conducted an extensive review of the available scientific literature and, in conclusion, approximated minimal clinically important differences (MCIDs) for various generic and disease specific outcome measures for both directly measured and patient reported outcomes, including TNSS. Data analysed by Barnes included three studies involving subjects suffering from PAR and SAR.

While the author concludes that there is much complexity surrounding the techniques used for the determination of MCIDs, benefits and limitations for each technique were presented and discussed. The technique applied to TNSS (anchor-based), is advocated in preference to surrogate approaches as it more directly establishes clinical importance.

The MCID for TNSS approximated 0.55 units, and further analysis indicated that there was no difference in the resulting MCID for PAR and SAR [Barnes M, 2006].[7]

A brief discussion regarding the treatment effect observed for Omnaris was presented and is based on the following key criteria:

1. The overall magnitude of benefit of Omnaris compared to baseline
2. The statistically significant treatment difference between Omnaris and placebo
3. Comparison of results with approved products within the same therapeutic class

SAR

The overall magnitude of benefit of Omnaris compared to baseline

In the Phase II and Phase III SAR studies, the overall magnitude of benefit for Omnaris 200 µg/day out of 12 points was -2.92 units in the Phase II study and –2.40 units in the pivotal Phase III study. If these changes are assessed in terms of symptom severity, the data show that patients transitioned from symptoms which were considered severe at baseline (9.40 and 8.96 for the TBN-CL-002 and M1-401 studies respectively) to moderate symptomology at study conclusion (6.5 and 6.6 for the TBN-CL-002 and M1-401 studies respectively).

It should be noted that the effect size reported for Omnaris was the effect over the *a priori* defined treatment period of 14 days and not on the last day of the treatment period (Day 14). Given the mechanism of action, it is not expected for a corticosteroid to achieve maximal benefit until after some period of treatment. A review of clinical studies

[6] United States Food and Drug Administration. Allergic Rhinitis: Clinical Development Programs for Drug Products, April 2000. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf

[7] Barnes ML, Minimal clinically important difference determination for common outcomes in Rhinology, Asthma & Allergy Research Group, MSc Thesis – Evidence Based Healthcare, Oxford University, Trinity Term September 2006.

conducted in SAR with other intranasal corticosteroids (INCS) reveals that the maximum benefit generally occurs about one to two weeks after the initiation of therapy. This is reflected in the Australian Product Information for various INCS where it is stated that the full clinical benefit may not be achieved in the first few days, or may take up to two weeks. [for example, Budamax Product Information, 2009; Nasonex Product Information, 2008]. Study results observed for Omnaris appear to support this mechanism of action as improvements in treatment effect continue to occur over time.

The statistically significant treatment difference between Omnaris and placebo

The estimated difference between Omnaris and placebo over the *a priori* specified primary analysis period of two weeks was 0.90.

Comparison of results with approved products within the same therapeutic class

The effect of Omnaris was also compared to the treatment effect for approved products within the therapeutic class in similarly designed studies. The magnitude of treatment effect observed with ciclesonide administered intranasally at a daily dose of 200 µg versus placebo is comparable to what has been shown previously with mometasone (Nasonex).[8] Among available INCS products, mometasone furoate employed the most similar scale in its pivotal efficacy study for measuring nasal symptoms to the one used in the ciclesonide program. In this study with mometasone furoate, the estimated difference from placebo in SAR was 0.8 (Nasonex) as compared to 0.9 with Omnaris. Additionally, the overall magnitude of benefit of 2.4 observed for ciclesonide was similar to the 2.3 observed in the pivotal mometasone SAR study.[8]

PAR

The overall magnitude of benefit of Omnaris compared to baseline

The magnitude of the treatment difference obtained in the PAR study (M1-402) was smaller than the effect size seen in the SAR studies (TBN-CL-002 and M1-401); this was not unexpected since the baseline symptom severity in PAR studies is typically lower than observed in SAR studies. In the two SAR studies, the mean baseline average AM and PM reflective TNSS values ranged from 8.8 to 9.4 across treatment groups, while in the PAR study, the mean baseline values were 7.6 and 7.7 on the 0-12 scale. In the long term safety study in PAR, the baseline symptom levels were even lower (6.4 units). The data support that lower rating of symptoms lead to smaller estimated treatment differences. In the M1-402 study, as in the M1-401 study, a relationship between baseline TNSS levels and estimated treatment difference was observed.

Additionally, the overall magnitude of improvement in the pivotal PAR study, –2.5 (33%), was similar to the benefit observed in the pivotal Phase III SAR study, -2.4 (27%), and the long-term safety study, –2.3 (36%). These changes in symptom scores in PAR represented a transition from moderate symptomology to mild to moderate (M1-402) or mild (M1-404) symptom severity by the end of the study, further supporting a clinically meaningful response.

The statistically significant treatment difference between Omnaris and placebo

As in SAR, it is expected that an initial treatment period is needed in order for a corticosteroid to reach maximal efficacy. The observed effect size for the average of the AM and PM reflective TNSS scores (the primary measure) continued to increase over the entire six week treatment period (0.42 for Days 1-14 [p=0.013]; 0.63 for Days 15-28

[8] United States FDA. Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray. Summary Basis of Approval, 1997. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020762_s000.pdf

[p=0.001] and 0.84 for Days 29-42 [p<0.001]). By the end of the M1-402 study on Day 42, the estimated treatment difference between ciclesonide 200 µg and placebo was 0.92 with a 95% CI of (0.60,1.80).

Comparison of results with approved products within the same therapeutic class

Comparisons of the results observed in the M1-402 and M1-404 PAR studies and those seen with other INCS clearly demonstrate that the effects seen with Omnaris are well within the range of those observed with other INCS [Weiner JM, 1998].[9] The four pivotal mometasone furoate studies supporting the registration of Nasonex showed estimated effect sizes ranging from 0.5 to 1.0.[8] Similarly, Avamys (fluticasone furoate) has also shown a similar effect size in PAR of 0.71. [Avamys Australian Product Information, March 2009].

Summary

Overall changes in TNSS from baseline reported in Omnaris studies (SAR and PAR) show an improvement in symptomatology (from severe to moderate or moderate to mild/moderate) and are hence indicative of a clinically meaningful benefit for individual patients.

The differences in treatment effect between Omnaris and placebo have been calculated based on a pooled analysis of available clinical study data for SAR and PAR. The results were 0.9 and 0.6 respectively. These values exceed the MCID of 0.55 defined by Barnes, 2006.[7]

The treatment effects observed for Omnaris are consistent with the treatment effects observed with other INCS.

In conclusion, the sponsor was confident that treatment with Omnaris results in significant and clinically meaningful benefits in the amelioration of the symptoms associated with AR.

Lack of active comparators

To date, the sponsor has not conducted any comparator studies with Omnaris since these were not required by the TGA to gain regulatory approval in Australia. The focus of the clinical development program for Omnaris was designed to meet the general safety and efficacy requirements outlined in the FDA guidance.[6] The US FDA approved Omnaris in October 2006. Approval was also received in Canada, Argentina, Brazil, Mexico, Korea, Hong Kong, Malaysia, Philippines and Taiwan. The pivotal Phase III study plan was discussed with the US FDA prior to the initiation of the studies.

Fourteen well controlled studies investigating the safety, efficacy and pharmacokinetic and pharmacodynamic profile of Omnaris have been conducted in healthy normal volunteers as well as patients with AR. These studies form the basis for the overall determination of efficacy and safety of Omnaris. Additionally, three studies conducted in Japanese subjects (in both healthy subjects and AR patients) provide supportive efficacy and safety data on the use of Omnaris. Studies in adolescent and adult patients, 12 years and older, included: a dose range finding study in SAR and two pivotal efficacy studies, one in SAR and one in PAR, three onset of action studies as well as three clinical studies that served to further characterise the safety of Omnaris related to long term safety as well as concomitant usage of Omnaris with inhaled corticosteroids.

[9] Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998; 317: 1624-29.

In the pivotal Phase III clinical studies for SAR and PAR, the changes from baseline in the average reflective AM and PM TNSS, the primary efficacy variable in these studies, demonstrated that Omnaris at a dose of 200 µg/day was effective in the treatment of nasal symptoms associated with SAR and PAR. The results from these pivotal studies confirmed the results obtained from the earlier Phase II dose ranging study conducted in patients with SAR and extended these results into the PAR population. In all 3 studies, Omnaris at a dose of 200 µg once daily produced a statistically significant reduction in symptom severity compared with placebo when measured by the primary efficacy variable. The magnitude of the treatment difference was similar between the SAR studies (0.82 on a 0-12 scale for the study by Ratner et al, 2006 (1) versus 0.90 for [Ratner, 2006 (2)] and somewhat smaller, as expected, in the PAR study by Chervinsky et al [0.63] due to the lower baseline values at study entry for this patient population.[10,11,12]

Although no direct head to head studies between Omnaris and other intranasal corticosteroid preparations have been conducted, given the fact that the same composite TNSS score was employed with the other INCS preparations, indirect cross study comparisons can be made. Among available INCS products, mometasone furoate employed the most similar scale for measuring nasal symptoms to the one used in the ciclesonide program. In the pivotal SAR and PAR efficacy studies with mometasone furoate, the estimated differences from placebo were 0.8 and 0.5, respectively, as compared to 0.9 and 0.6, respectively, for Omnaris.[8] The treatment effect size observed between ciclesonide and placebo for the PAR study of 0.63 was also within the range generally seen in other PAR studies reported for other intranasal corticosteroid preparations [Weiner JM, 1998].[9] Although it is not appropriate to make definitive conclusions based upon these indirect comparisons, these data support the tenant that the efficacy of Omnaris is within the range of other corticosteroid preparations currently available in the marketplace.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, expressed its view that the overall risk benefit profile for this product was negative. The ACPM considered the following matters:

The ACPM agreed with the delegate that there were no unresolved quality, pharmaceutical chemistry, bioavailability or nonclinical concerns.

Efficacy

The ACPM was concerned that the efficacy of this product is only established against placebo and that the absolute effect size is small and clinically marginal, when compared to placebo, even in adults. The committee also agreed with the Delegate that the lack of efficacy data against active comparators, as suggested by the TGA-adopted EU guideline, is a further significant deficiency. In addition, there was a lack of data on the maintenance of efficacy for these indications and of data on prevention of relapses in PAR.

[10] Ratner PH, Wingertzahn MA, van Bavel JH et al. Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2006; 97: 657-663.

[11] Ratner PH, Wingertzahn MA, van Bavel JH, Hampel F, Darken PF, Shah T. Efficacy and safety of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2006; 118: 1142-48.

[12] Chervinsky P, Kunjibettu S, Miller DL et al. Long term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. Ann Asthma Allergy Immunol 2007; 99: 69-76.

Safety

There were no particular safety signals of concern noted. Despite 4 reported events related to depression, suicidal ideation or drug overdose, overall, the serious adverse events did not reveal any trends as they were isolated events. The adverse events in subjects less than 12 years were similar between active and placebo groups. No studies assessing the effect of ciclesonide nasal spray on growth have been conducted. The incidence of discontinuation was similar for the intranasal ciclesonide 200 µg group as for placebo.

The ACPM was also concerned that the safety and efficacy data submitted refer only to short term use, whereas patients may well use the product for a considerable period.

Initial Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application for a new dose form, new route of administration and extension of indications for ciclesonide.

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Application

The Delegate of the Minister noted that the quality and nonclinical reviews raised no objections to registration.

The clinical evaluator conducted a comprehensive review of the clinical data submitted and recommended approval of the product for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and older, and for the treatment of perennial allergic rhinitis in adults and adolescents 12 years of age and older.

In terms of benefit the clinical evaluator concluded that "efficacy was demonstrated in adult subjects with both PAR and SAR" and that "in children aged 6 to 11 years with SAR there were improvements in TNSS and PANS with the 200 µg dose and in the same age group, "with PAR there was an increasing effect with increasing doses up to 200 µg/day, with no plateau effect."

The evaluator reported that "the improvement in TNSS with intranasal ciclesonide 200 µg/day have been demonstrated through to 52 weeks in subjects with PAR."

In the context of efficacy the evaluator noted that "the design of the clinical studies conformed with" the TGA-adopted EU guideline on the treatment of allergic rhino-conjuctivitis.[3]

In terms of risk the evaluator concluded that "intranasal ciclesonide appears to be well tolerated and to have a good safety profile." The evaluator reported that the sponsor had conducted studies of the effect of intranasal ciclesonide on HPA axis, which is a surrogate measure for suppression of growth by steroids and steroid like substances. Studies to measure long term growth take many years and are not usually performed for an initial submission package. The evaluator noted that "intranasal ciclesonide did not appear to have significant effects upon the HPA axis .. "

The evaluator in discussing safety also noted that "in total 1777 subjects have been exposed to intranasal ciclesonide 200 µg daily .... This includes 198 subjects under the age of 12 years. The approximate total exposure to ciclesonide 200 µg was 450 patient years and 97 subjects were exposed for one year or more".

In considering the balance of efficacy and safety of the product the evaluator noted that "intranasal ciclesonide has a favourable safety profile, so notwithstanding that the clinical significance of the treatment effect is not clear, the risk benefit assessment is in favour of ciclesonide"

The Delegate of the Secretary sought the advice of the Advisory Committee on Prescription Medicines (ACPM) who considered the application on 1 July 2011. In her notes for the committee the Delegate commented:

1. The efficacy of this product is only established against placebo and the absolute effect size is rather small, even in adults.
2. The lack of active comparative is a significant deficiency.
3. The maintenance of efficacy for these indications or whether the use of this agent prevents relapses in PAR is not known. This may cause some concern in regard to the approvability of Omnaris in PAR.
4. No specific safety concerns arise from this data package.

The Delegate further indicated her proposed intention to approve the product.

The ACPM resolved that the overall risk benefit profile for this product was negative. In reaching this conclusion the Committee said it considered the following:

Efficacy

The ACPM was concerned that the efficacy of this product is only established against placebo and that the absolute effect size is small and clinically marginal, when compared to placebo, even in adults. The committee also agreed with the Delegate that the lack of efficacy data against active comparators, suggested by TGA-adopted EU guidelines, is a further significant deficiency. In addition, there was a lack of data on the maintenance of efficacy for these indications and of data on prevention of relapses in PAR.

Safety

There were no particular safety signals of concern noted. Despite 4 reported adverse events related to depression, suicidal ideation or drug overdose, overall the serious adverse events did not reveal any trends as they were isolated events. The adverse events in subjects less than 12 years were similar between active and placebo groups. No studies assessing the effect of ciclesonide nasal spray on growth have been conducted. The incidence of discontinuation was similar for the intranasal ciclesonide 200 µg group as for placebo.

The initial decision

On 1 July 2011 the Delegate of the Secretary notified the sponsor of her decision to refuse the application for inclusion of the product in the Australian Register of Therapeutic Goods (ARTG).

On 12 July 2011 she provided the applicant with the reason for her decision. These were:

1. Lack of adequate efficacy;

· The pivotal studies submitted to support efficacy in SAR and PA showed small differences in relation to the primary efficacy endpoint, between ciclesonide and placebo groups which were clinically insignificant. That is, Omnaris was not shown to be better than no active treatment in these studies.

· There were no efficacy studies with active comparators. This is problematical because there is no possibility of demonstrating non-inferiority or superiority to a registered comparator.

- There were no long term efficacy data and this is relevant as this product may be taken long term.

2. Inadequate safety data;

- There were no long term safety data and this is significant as this product is likely to be taken over long periods for the proposed indications.

The Appeal

In a letter dated 27 September 2011 the sponsor lodged an appeal to the Parliamentary Secretary. The grounds for the appeal related to arguments on deficiencies in the decision making process and inadequate evaluation of the scientific data and arguments in relation to these were set out comprehensively in the appeal document over 15 pages. In addition the appeal contained a supporting letter of opinion from a Professor of Immunology and Allergy.

Consideration of the appeal

The Delegate of the Minister considered the material contained on the files in relation to the application to register Omnaris, including evaluations of the data submitted to establish the safety and efficacy of the product, the applicants pre-ACPM response package, the material submitted as part of the appeal package including the arguments made in support of registration, and the Risk Management Plan (RMP) assessment completed November 2011.

The Delegate of the Minister considered the legislative requirements for inclusion of a registered medicine in the ARTG, the material set out as findings of fact and TGA-adopted guideline on product development for allergic rhinoconjunctivitis.[3]

The Delegate of the Minister concluded that there is evidence of safety and efficacy, including for use in perennial allergic rhinitis (PAR) in the long term (52 weeks) and this has been acknowledged at various points by the TGA evaluator and/or the Delegate of the Secretary. The Delegate of the Minister reviewed the requirements of Section 25 of the Act and believed the criteria for inclusion of a therapeutic good on the ARTG have been met. The Delegate of the Minister considered the TGA-adopted EU guideline and noted that it is not superior to the legislative requirements but that it represents reasonable consensus as to what constitutes acceptable evidence. The Delegate of the Minister agreed with the clinical evaluator that the studies submitted do comply with the requirements set out in the guideline.

The legislation sets out the criteria of decision making in respect of applications for inclusion of a good on the ARTG. The assessment by the Delegate of the Minister of the material on file and contained within the appeal documentation convinced the Delegate that these criteria have been met.

The Delegate of the Minister therefore have decided to revoke the initial decision of and replaced it with one to approve the inclusion of Omnaris (ciclesonide) 50 µg /actuation Nasal Spray in the ARTG for the indication:

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.*

Included among specific conditions of registration was the implementation in Australia of the ciclesonide Risk Management Plan (RMP), dated 15 November 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

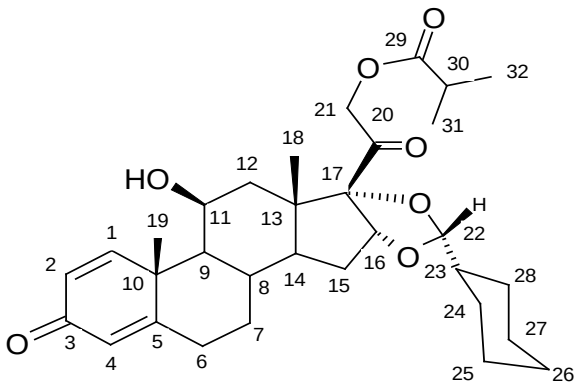
OMNARIS® NASAL SPRAY

PRODUCT INFORMATION

NAME OF THE MEDICINE

Ciclesonide

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)-,(11b,16a)-. Ciclesonide is delivered as the R-epimer [CAS: 126544-47-6]. The empirical formula is $C_{32}H_{44}O_7$ and its molecular weight is 540.7. Its structural formula is as follows:



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 microcrystalline cellulose, 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 C_{max} 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 pediatric 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.

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 µg ex-actuator ciclesonide by oral inhalation and dose adjustment in liver impairment is not necessary.

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 form 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 trials. 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 form 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

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

PRECAUTIONS

Immune System

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, 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.

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.

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

Systemic Effects

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. 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.

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 embryofetal 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 embryofetal 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 fetal weight. Ciclesonide increased fetal 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, fetus 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.

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 tumor) 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).

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.

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 a 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 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.

Effects on Laboratory Tests

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

ADVERSE EFFECTS

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

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

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

Nervous System: dysgeusia (0.2%)

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

* occurred at rates ≤ placebo

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, randomized 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 40µg 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, and dyspnoea, 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

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

Nycomed Pty Ltd
2-4 Lyonpark Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

DATE OF APPROVAL

Date of TGA approval: 28 November 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

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